



# THE AMERICAN HEART JOURNAL



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A JOURNAL FOR THE STUDY OF THE CIRCULATION

PUBLISHED MONTHLY

UNDER THE EDITORIAL DIRECTION OF  
THE AMERICAN HEART ASSOCIATION

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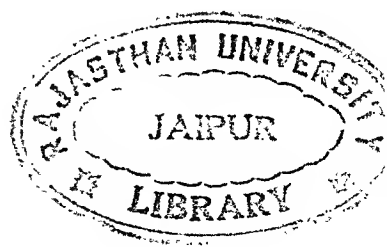
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VOLUME 14  
JULY—DECEMBER, 1937

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ST. LOUIS  
THE C. V. MOSBY COMPANY

1937





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Press of  
The C. V. Mosby Company  
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# The American Heart Journal

VOL. 14

JULY, 1937

No. 1

## Original Communications

### SOME REMARKS ON THE TECHNIQUE IN CLINICAL ELECTROCARDIOGRAPHY WITH PRECORDIAL DERIVATION\*

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**A**MONG other properties the following have contributed to the hitherto prevailing employment of derivations from the extremities in clinical electrocardiography: 1. The relatively uniform appearance of these derivatives in normal persons, e.g., the P- and T-waves are always positive in Leads I and II. 2. Their constant form on repeated examinations of the same person, owing to the fact that even considerable changes in the localization of the electrodes on the extremities and in the position of the subject give but very slight changes in the form of the curves.

In the choice of precordial derivations for routine employment it will be expedient to select leads that have the same properties as far as possible.

The precordial derivations now employed are all "semidirect" (Wilson and associates<sup>11</sup>) or "unipolar" (Groedel<sup>3</sup>), meaning that one electrode (the principal) is placed on the precordium (just over the heart or in its immediate vicinity), while the other electrode (the indifferent) is placed so far away from the heart that the variations of potential at that point are very small in proportion to the variations on the principal electrode. The ideal would be an indifferent electrode with the potential constantly = 0. But the human body has no region where every individual shows complete absence of potential variations due to the heart action. Nor is an ideal zero electrode obtainable after the method given by Wilson and collaborators<sup>12</sup> or by Storti.<sup>10</sup>

The significance of the location of the indifferent electrode to the form of the electrocardiogram is evident from Figure 1, which shows different precordial derivations in a man, aged twenty-one years, with-

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out any circulatory disturbance. All the electrocardiograms are taken with the amplifier electrocardiograph described earlier by Larsen.<sup>5</sup> Each picture shows two derivations taken at the same time. No change whatever was made in the location of the *principal* electrode, while the place of the *indifferent* electrode was varied as recorded in the legend of the figure. It will be noticed that the P- and T-waves in both derivations are distinctly positive when the indifferent electrode is placed on the right arm, while this is not the case with the other localizations. (In *B*, Td is "humpy," in *C*, Ps is isoelectric, in *E*, Td is "humpy," and in *F*, Pd and Ps are diphasic, Td, negative.) Examination of five other normal subjects showed similar conditions. If we wish to employ only one localization of the indifferent electrode, it will therefore, according to the view set forth in the introduction, appear to be most expedient to choose the electrode of the right arm for indifferent electrode. It has been my experience with a few hundred normal adults that, with this localization of the indifferent electrode, the P- and T-waves always are positive—at any rate with the given localizations of the principal electrode. That other localizations of the in-

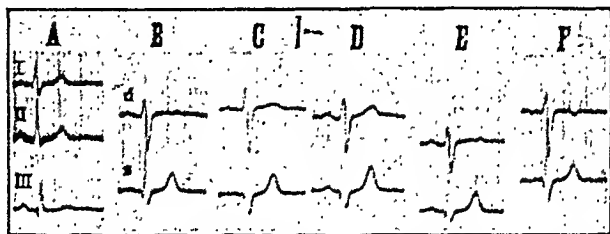


Fig. 1.—Derivations from the extremities and various semidirect precordial derivations in a man aged twenty-one years, without circulatory disturbances.

*A*: Derivations from the extremities.

*B-F*: Precordial derivations. In derivation *d* the different electrode was placed every time at the lower left corner of the sternum, in derivation *s* it was placed every time with its center 4 cm. lateral to, and at a level with, the apex of the heart. The indifferent electrode in *B* was Wilson's electrode,\* in *C* it was an electrode at the angle of the right scapula, in *D* it was the electrode on the right arm, in *E*, the electrode on the left arm, and in *F*, the electrode on the left leg.

Timer = 0.05 sec. 1 millivolt = ca. 20 mm. in the original.

different electrode give a more variable form to the P- and T-waves is also evident from the studies on normal adults reported by Goldbloom,<sup>2</sup> Katz and Kissin,<sup>4</sup> Master,<sup>7</sup> and Shipley and Hallaran.<sup>9</sup> To use the right-arm electrode for indifferent electrode also offers the advantage that the deflections become greater in this way than with any other localization of the indifferent electrode (Einthoven and de Lint,<sup>1</sup> Roth,<sup>8</sup> the writer's own experience).

As to the localization of the principal electrode it may be said generally that larger waves are obtained by derivation from the precordium proper than by derivation a little outside the heart borders, and that a displacement of the electrode in the former location gives

\*Wilson's<sup>12</sup> electrode is formed by joining the electrodes on the right arm, left arm, and left leg through resistances of 5,000 ohms (in our clinic 10,000 ohms) and using this junction for indifferent electrode.

greater changes in the form of the electrocardiograms than does an equal linear displacement of the electrode in the latter place. The last point is illustrated plainly in Figure 2 (note legend); examination of two other persons showed similar conditions. So it is to be

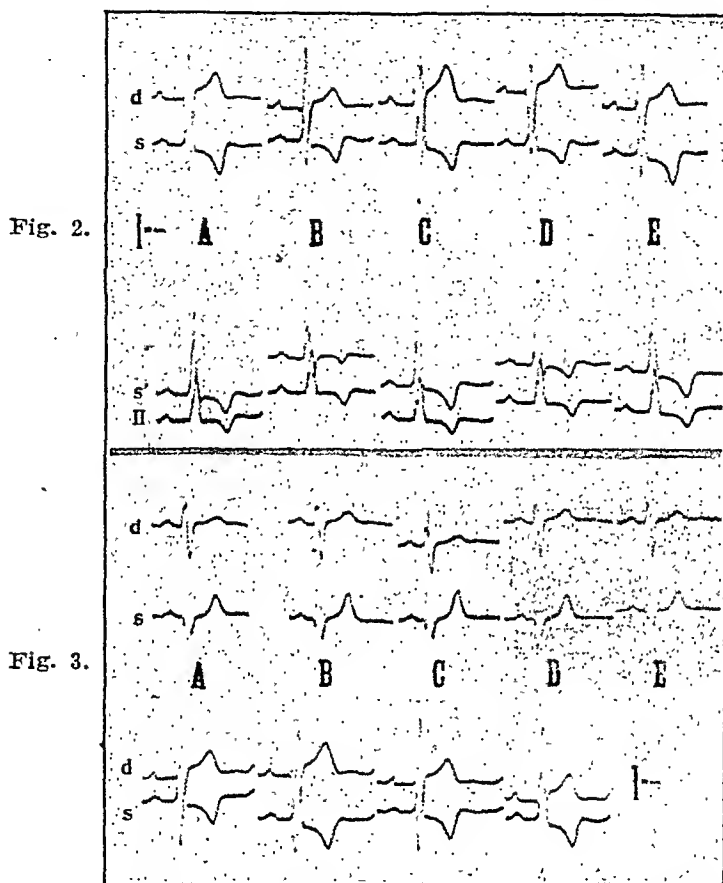


Fig. 2.

Fig. 3.

Fig. 2.—Precordial derivations from a man, aged thirty-five years, with rheumatic aortic disease.

In A the principal electrode in Lead *d* was placed at the lower left corner of the sternum, in Lead *s* its center was localized 4 cm. lateral to, and at a level with, the apex of the heart, in Lead *s'* it was placed over the apex of the heart. The electrode on the right arm served as indifferent electrode. In the following records (B-E) the electrodes are shifted (electrode *d*: 1.5 cm. electrodes *s* and *s'*: 3 cm.) respectively to the right in B, to the left in C, upwards in D, and downwards in E.

In this way, Lead *s'* shows greater variations than Lead *s*.

Timer = 0.05 sec. 1 millivolt = ca. 20 mm. in the original.

SIZE OF THE MORE IMPORTANT WAVES IN FIGURE 2, IN MM.

LOCALIZATION OF ELECTRODES	Rd	Sd	Td	Rs	Ss	Ts	Rs'	Ss'	Ts'
A. d: Lower left sternal angle s: 4 cm. lateral to apex of heart s': Apex of heart	1.3	42.0	15.3	51.8	0	16.8	49.0	4.6	10.0
B. Shift to right	0.5	32.0	11.2	53.0	sug- gest.	12.6	19.5	10.0	2.8
C. Shift to left	9.0	57.5	23.0	45.5	0	14.7	57.0	sug- gest.	14.2
D. Shift upwards	1.5	35.5	15.0	46.0	sug- gest.	10.7	49.0	5.8	7.8
E. Shift downwards	4.4	38.0	13.3	50.6	0	17.0	43.0	2.8	13.0

Fig. 3.—The upper row shows the precordial derivations *d* and *s* in a man, aged twenty-one years, without circulatory disturbances, the lower row shows the same derivations in a man aged thirty-five years, with rheumatic aortic disease.

In A the subject is lying on his back (ordinary posture), in B he is half lying on his right side, C, half lying on his left side, D, half sitting, E, sitting.

Timer = 0.05 sec. 1 millivolt = ca. 20 mm. in the original.

pointed out that derivation from a place a little lateral to the apex of the heart implies a greater possibility of uniformity of the curves, on repeated examinations, than may be obtained with derivation from the apex of the heart.

The localizations most commonly employed for the principal electrode are the apex of the heart and the left fourth intercostal space, just at the border of the sternum. The writer employs the derivations given by Groedel,<sup>3</sup> namely: from the lower left corner of the sternum to the right arm (Lead *d*), and from a point (i.e., the center of the electrode) 4 cm. lateral to, and at a level with, the apex of the heart to the right arm (Lead *s*). Groedel takes his derivations to present potential variations in relation to the variations of potential in the right and left ventricles, respectively. Figure 3 illustrates how little the form of the electrocardiograms with these derivations is influenced by differences in the positions of the subjects (note legend). Forced breathing

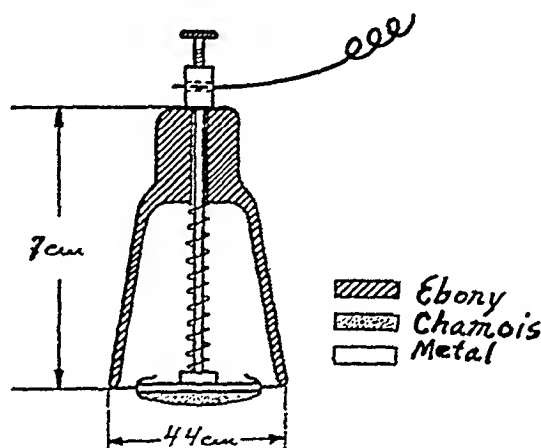


Fig. 4.—Electrode for the taking of precordial derivations.

and slow deep breathing gave no particular changes in the curves. For particular study of the P-wave (block and auricular fibrillation) the writer uses a derivation from the right third intercostal space, just at the sternal margin, to the right arm.

In routine electrocardiography with precordial derivations, the electrode depicted in Figure 4 has been of great help to us. After the derivations from the extremities are taken in the usual manner, the left-arm lead of the electrocardiograph is fastened—in keeping with the rule formulated by Larsen and Warburg<sup>6</sup>—to the precordial electrode, and the desired precordial derivation is taken as Lead I. The method requires an assistant to hold the electrode firmly against the given spot on the thorax—but anybody present may serve as assistant. The diameter of the metal plate is 3 cm. There will hardly be any reason to use electrodes of smaller diameters; besides, smaller diameters would also make it more difficult to make the curves look alike on repeated examinations, for it is found that, with equal linear displace-

ment of a large electrode and a small one (i.e., displacement of their centers), the smaller electrode gives greater changes in the form of the curves than does the large electrode. An example of this is shown in Figure 5 (note legend), and the same was found on examination of two other persons.

## SUMMARY

The most favorable localization of the indifferent electrode in semi-direct precordial derivations is the right arm, because this localization gives a more uniform appearance of the electrocardiograms of normal adults and greater deflections than other localizations of the indifferent electrode.

It is shown that the form of the precordial derivations *d* and *s* given by Groedel is only little changed by minor variations in the position of the patient and in the localization of the electrodes.

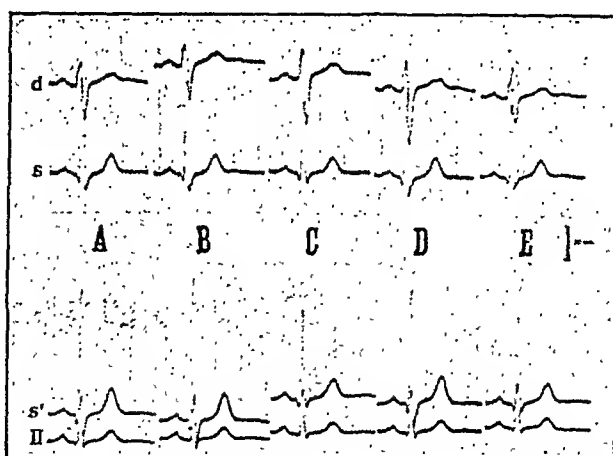


Fig. 5.—Precordial electrocardiograms from a man, aged twenty-one years, without circulatory disturbances.

Upper row: A gives the derivations *d* and *s*. In the following pictures (B-E) the centers of the electrodes have been shifted—electrode *d*, 1.5 cm., electrode *s*, 3 cm., respectively, to the right in B, to the left in C, upwards in D, and downwards in E. An electrode of 6 cm. in diameter was used in taking derivation *s*.

Lower row: An electrode of 3 cm. is used in taking derivation *s'*, the center of this electrode being placed on the points where the center of electrode *s* was placed in taking the upper row.

On comparison of derivations *s* and *s'*, the variations on the size of the waves are seen to the greatest in derivation *s'*.

Timer = 0.05 sec. 1 millivolt = ca. 20 mm. in the original.

SIZE OF THE MORE IMPORTANT WAVES IN FIGURE 5, IN MM.

LOCALIZATION OF ELECTRODES	Rd	SD	Td	RS	Ss	Ts	Rs'	Ss'	Ts'
d: Lower left sternal angle		—			—			—	
A. s: 4 cm. lateral to apex of heart	13	18.5	6.3	56.0	9.5	12	73.5	12.0	16
s': 4 cm. lateral to apex of heart									
B. Shift to right	11	19.0	7.0	55.0	8.5	12	84.0	13.0	17
C. Shift to left	16	27.0	8.0	43.0	5.0	10	53.0	4.5	12
D. Shift upwards	18	31.5	6.0	53.5	9.0	12	68.0	11.5	16
E. Shift downwards	17	14.5	8.0	43.0	6.0	10	52.0	5.5	12

A handy electrode for the routine taking of precordial derivations is shown, and the effects of variations in the size of the electrode are demonstrated.

## REFERENCES

1. Einthoven, W., and de Lint, K.: *Arch. f. d. ges. Physiol.* 80: 150, 1900.
2. Goldbloom, A. A.: *Am. J. M. Sc.* 187: 489, 1934.
3. Groedel, F. M.: *Das Extremitäten-, Thorax und Partialekg. des Menschen*, Th. Steinkopff, Dresden und Leipzig, 1934.
4. Katz, L. N., and Kissin, M.: *AM. HEART J.* 8: 595, 1933.
5. Larsen, Kaj H.: *Acta med. Scandinav.*, Suppl. 78: 141, 1936.
6. Larsen, Kaj H., and Warburg, E.: *AM. HEART J.* 14: 7, 1937.
7. Master, A. M.: *AM. HEART J.* 9: 511, 1934.
8. Roth, J. R.: *AM. HEART J.* 10: 798, 1935.
9. Shipley, R. A., and Hallaran, W. R.: *AM. HEART J.* 11: 325, 1936.
10. Storti, E.: *Ztschr. f. Kreislaufforsch.* 27: 830, 1935.
11. Wilson, F. N., Macleod, A. G., and Barker, P. S.: *AM. HEART J.* 7: 305, 1932.
12. Wilson, F. N., Johnston, F. D., McLeod, A. G., and Barker, P. S.: *AM. HEART J.* 9: 447, 1934.

# A RATIONAL PRINCIPLE FOR THE CONNECTIONS OF THE LEADS OF THE ELECTROCARDIOGRAPH IN CLINICAL ELECTROCARDIOGRAPHY WITH PRECORDIAL DERIVATION\*

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SINCE Wolferth and Wood<sup>16, 17, 18, 19</sup> in 1932 and 1933 reported their employment of precordial derivations in clinical electrocardiography, this question has attracted considerable interest, as is evident from a great number of papers from all parts of the world. Under the circumstances therefore it is highly desirable that a uniform technique for the taking of precordial electrocardiograms should be adopted in order that tracings everywhere may be standardized and comparable.

Wolferth and Wood connect the lead of the electrocardiograph for the right arm to the principal electrode (nearest the heart), and the lead for the left leg to the indifferent (remote) electrode; with such a connection, the T-wave in normal adults is inverted, and hence the electrocardiogram will look like a mirror image when compared with the leads from the extremities. A great many investigators have employed this connection of the leads, e.g., Goldbloom,<sup>3</sup> Hoffman and Delong,<sup>5</sup> Katz and Kissin,<sup>7</sup> Levy and Brucnn,<sup>9</sup> Master,<sup>11</sup> Rosenblum and Sampson,<sup>12</sup> Shipley and Hallaran,<sup>14</sup> and Wilson and his associates.<sup>15</sup> Others have found it more practical and in principle more proper to have the normal T-wave recorded in the same direction in precordial derivations as in derivations from the extremities, and hence they have arranged the leads reversely, i.e., have connected the lead for the right arm to the indifferent electrode and the lead for the left arm or left leg to the precordial electrode—as is done, among others, by Groedel,<sup>4</sup> Jervell,<sup>6</sup> Liberson and Liberson,<sup>10</sup> and Roth.<sup>13</sup> No doubt, one can accustom oneself to normal negative T-waves (i.e., downward deflections of the curve) as well as to normal positive T-waves, but it takes a very considerable training in reading electrocardiograms as fast and correctly as usual, if they are taken now in one way, then in another. Moreover, as long as there is no established rule for this procedure, one must always have information about the connection of the leads.

As is well known, Einthoven<sup>1, 2</sup> followed the rule that the connection of the leads, the polarity of the galvanometer, and the direction of the

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movement of the photographic film shall agree mutually in such a way that a negative potential impressed upon the right-hand or cranial electrode is registered on the curve as an upward deflection, when the curve is read from the start (at the left) toward the right. This principle is not directly applicable to precordial derivations, however, for then a negative potential impressed on the precordial electrode will be registered as an upward deflection of the curve if the indifferent electrode is localized to the left or caudally to the precordium (for example on the left leg), but as a downward wave if the indifferent electrode is localized to the right or cranially to the precordium (e.g., on the right arm). As it is agreed in general that the variations of potential at the precordial electrode are so great in proportion to the variations of potential at the indifferent electrode as to determine in all essentials the appearance of the precordial electrocardiogram, it seems irrational that this dominating potential in some precordial derivations is registered as an upward wave on the curve, in others as a downward wave. On the other hand, it would be a rational thing to adopt the following rule:

*The connection of the leads, the polarity of the galvanometer and the direction of the movement of the photographic film are to agree mutually in such a way that a negative potential impressed on the (chest) electrode is recorded on the curve as a downward deflection, the curve being read from the start (at left) toward the right.*

This is in keeping with the general principles of graphic recording. This rule is observed if, on an ordinary electrocardiogram, the lead for the right arm is connected to the indifferent electrode, while one of the other leads is connected to the principal electrode.

The leads employed by Wolferth and Wood are contrary to the above rule, as an upward deflection of the curve in their electrocardiogram means that the precordial electrode has been negative in relation to the indifferent electrode. Wolferth and Wood adopted this method because they wanted the greatest possible similarity between their curves from patients with infarction of the heart and their curves from animals with experimental infarcts, and in their introductory animal experiments, for no given reasons, these investigators had connected the lead for the right arm to the principal electrode.

By following the rule enunciated above we get precordial electrocardiograms to which the nomenclature given by Einthoven,<sup>1</sup> and now employed everywhere, is directly applicable; whereas this is associated with some difficulties in precordial electrocardiograms taken with the opposite connection of the leads. After Einthoven, the first wave in the initial complex is designated as Q if it points downward, and as R if it points upward, while a downward wave that comes after an upward is designated as S, as S is also designated the downward wave

in cases when there is no upward wave at all. In normal persons, as is well known, R is the most constant and highest wave in the initial complex in derivations from the extremities.

That this is the case also in many precordial leads taken according to the rule given above, is evident from illustrations presented in a paper on precordial leads by Kaj H. Larsen.<sup>8</sup> If the electrocardiograms shown in these pictures had been taken with the opposite connection of the leads, the most constant and greatest wave in the initial complex would have pointed downward, and then it would have to be designated, after Einthoven, as Q or S, depending on whether or not it was preceded by an upward wave. But to designate this constant wave as Q or S must be said to be irrational, as in reality it is an R-wave, being synchronous with the R-waves in derivations from the extremities. This is seen in synchronous electrocardiograms taken with precordial derivation and with derivation from the extremities as shown, for example, in the aforementioned paper by Kaj H. Larsen, Fig. 5, lower row.

#### SUMMARY

A hard and fast rule for the making of precordial electrocardiograms has been given which insures that the direction of the waves will be in conformity with the rules generally applied to the registration of events in the standard leads.

#### REFERENCES

1. Einthoven, W.: *Arch. f. d. ges. Physiol.* 60: 101, 1895.
2. Einthoven, W.: *Arch. f. d. ges. Physiol.* 122: 527, 1908.
3. Goldbloom, A. A.: *Am. J. M. Sc.* 187: 489, 1934.
4. Groedel, F. M.: *Das Extremitäten-Thorax und Partialekg. des Menschen*, Th. Steinkopff, Dresden und Leipzig, 1934.
5. Hoffman, A. M., and Delong, E.: *Arch. Int. Med.* 51: 947, 1933.
6. Jervell, A.: *Acta med. Scandinav. Suppl.* LXVIII, 1935.
7. Katz, L. N., and Kissin, M.: *AM. HEART J.* 8: 595, 1933.
8. Larsen, Kaj H.: *AM. HEART J.* 14: 1, 1937.
9. Levy, R. L., and Bruenn, H. G.: *AM. HEART J.* 10: 881, 1935.
10. Liberson, A., and Liberson, F.: *Ann. Int. Med.* 6: 1315, 1933.
11. Master, A. M.: *AM. HEART J.* 9: 511, 1934.
12. Rosenblum, H., and Sampson, J. J.: *AM. HEART J.* 11: 49, 1936.
13. Roth, J. R.: *AM. HEART J.* 10: 798, 1935.
14. Shipley, R. A., and Hallaran, W. R.: *AM. HEART J.* 11: 325, 1936.
15. Wilson, F. N., McLeod, A. G., and Barker, P. S.: *AM. HEART J.* 7: 305, 1932.
16. Wolferth, C. C., and Wood, F. C.: *Am. J. M. Sc.* 183: 30, 1932.
17. Wolferth, C. C., and Wood, F. C.: *M. Clin. North America* 16: 161, 1932.
18. Wood, F. C., and Wolferth, C. C.: *Arch. Int. Med.* 51: 771, 1933.
19. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: *Arch. Int. Med.* 52: 752, 1933.

## HEART MURMURS

FROM THE VIEWPOINT OF AN ACTUARY

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RECENTLY I had occasion to review the medical literature on the subject of heart murmurs, with especial regard to the effect on longevity. To my surprise I was unable to find any comparison made by a heart specialist of the death rates among persons with heart murmurs in relation to the normal mortality, i.e., no statement had appeared of the extra mortality based on experience. Moreover, I did not see any reference to the extensive investigations made by the life insurance companies, through the cooperation of their medical directors and actuaries. The purpose of this article is to give the medical profession a synopsis of the mortality experiences of these companies, prepared without bias and forming the bases for the insurance of lives for many millions of dollars.

Probably the reason for the failure to refer to medico-actuarial investigations is that physicians and surgeons do not sufficiently understand the object sought, the nature of the material available for study, and the method used in presenting the results of the analysis, each of which I shall now consider. With regard to the first mentioned, the companies desire to obtain information which will enable them to value the applicant's prospect of longevity; accordingly it is necessary to segregate the cases in which there apparently is organic disease and those with the so-called functional murmur. The companies can then determine what cases should be accepted at the regular rate of premium and which should be charged an extra premium on account of the additional hazard. This involves the valuation of applicants with heart defects according to the history and the physical signs. What is the meaning of a murmur? To what extent will statistics show that the longevity is modified by the presence of an abnormality? Is it scientifically possible to place the applicants in groups according to the deviations from standards accepted as normal and to insure them on a basis which is fair to them and to the company?

*Cooperative Investigation.*—With regard to the material available for study, life insurance companies have separate departments for mortality investigations and have records based on codes covering a large number of lives, such records being in the shape of perforated cards handled by modern machinery. They can follow the policyholder

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\*Vice president and chief actuary, New York Life Insurance Co.

until death, at which time the cause is obtained, or until he gives up his policy. For a generation the life insurance companies have been making cooperative studies, combining their material, and since 1909 there has been a committee of actuaries from the Actuarial Society of America and of physicians from the Association of Life Insurance Medical Directors in charge of these statistical researches. During that period many reports have been published, covering persons with all the principal types of impairment and those in hundreds of occupations involving hazard. For example, the volumes published in 1931 and 1932, entitled "Medical Impairment Study" (hereafter designated as M.I.S.), covered 2,100,000 policies in 125 groups or classes, involving, for instance, persons with heart murmurs, tuberculous family history, high blood pressure, rapid pulse, albuminuria, those with a history of renal colic, syphilis, gastric ulcers and all the gamut of human afflictions.

*Method of Determining the Relative Mortality.*—The method of presenting the statistics is very simple and does not require technical knowledge to understand. All that the readers need to know is that the mortality for the class under consideration is expressed in relation to the normal mortality, which is the death rate among "standard" risks.

At this point let me state that "standard risks" are those presenting no impairments or such minor ones that they are accepted at the regular premium rates, while "substandard" are those which present impairments of a more serious nature and hence are charged an extra premium or limited in some other way. If, for example, the relative mortality, taking account of the age of the insured and the duration of the insurance, was stated to be 150 per cent, it means 50 per cent higher than the normal or standard mortality; and this is the same as an extra death rate of 50 per cent. Thus, if the *extra* mortality among persons with a certain type of heart murmur was 50 per cent, then the companies had 50 per cent more deaths than among a corresponding group of lives considered to be "standard" or normal. Another way to look at the method of recording relative mortality is, that if the extra mortality were 50 per cent then there would be 150 deaths in the heart group against 100 in a similar group of the same ages and duration of insurance but without that impairment. In this article I shall always refer to the extra mortality in each class. The physician in reading this article need not concern himself with the various mortality tables used in determining the normal death rate. The general mortality of the insurance companies has improved but the ratios now presented take account of such changes. From the foregoing explanation it will be seen that the mortality among "standard lives" represents the "control" group against which all abnormal classes are measured.

In dealing with the mortality I refer to that from all causes among persons, who, when insured, showed some abnormality of the cardiovascular system. In several of the classes the death rate from heart disease will be given.

*Nomenclature.*—With the purpose of separating the applicants having organic heart disease from those without it, the insurance companies, in the years prior to 1925, coded heart murmurs under functional, mitral regurgitation, aortic regurgitation, and aortic obstruction. The clinical criteria for separating organic heart disease from nonorganic or functional are not well defined. For example, given a systolic murmur at the apex, does the fact that the murmur is transmitted lend weight to the probability that the murmur is caused by an organic defect? Or again is the same kind of a murmur associated with enlargement of the heart more significant than when this murmur is found in a heart of normal size? It was questions of this nature that led the companies in 1925 to adopt a new method of coding. In that year they began to regard the heart impairments according to the clinical description of the murmur found by the medical examiner. An outline is presented in which the old and new methods of classification are compared approximately:

CLASSIFICATION PRIOR TO 1925	CLASSIFICATION OF 1925 AND LATER
Functional Murmurs	Apex murmur, systolic, constant, not transmitted. Apex murmur, systolic, inconstant. Basic murmur, aortic area, systolic, constant, not transmitted. Basic murmur, aortic area, systolic, inconstant. Basic murmur, pulmonic area, systolic, constant, not transmitted.
Mitral Regurgitation	Apex murmur, systolic, constant, transmitted to the left.
Mitral Obstruction	Apex murmur, presystolic or diastolic, constant.
Aortic Obstruction	Basic murmur, aortic area, systolic, constant, transmitted upward.
Aortic Regurgitation	Basic murmur, aortic area, diastolic, constant, transmitted downward.

To aid in understanding the methods of the companies a special form of medical examination in connection with the heart appears in the appendix.\*

\*Special instructions for examination of the circulatory system are given in a booklet issued by the medical department for the guidance of our examiners in making examinations for the company. A copy of these instructions is included in the appendix.

## RESULTS OF STUDIES

In order to give an idea of the importance to be attached to each group, the number of deaths will be shown. In Table I the two principal classes in this study (M.I.S.) of the so-called functional murmurs are given separately and the other two are combined—all cases being without hypertrophy.

TABLE I

TYPE OF MURMUR—NOT TRANSMITTED	NUMBER OF DEATHS	EXTRA MORTALITY OVER NORMAL, %
A. Constant systolic apex murmur	234	56
B. Constant systolic basic murmur, pulmonic area	124	12
C. Inconstant systolic apex murmur, also constant systolic basic murmur, aortic area	94	35

A fifth class closely related to these—inconstant systolic basic murmur in the aortic area was not studied in the M.I.S.

An interpretation of Table I may be of value at this point. The deaths among persons with a constant systolic apex murmur, not transmitted, were 234 but there would have been only 150 in a corresponding group without that impairment. Therefore the relative mortality was 156 per cent or an extra death rate of 56 per cent.

The material in Table I included only those lives which had been charged an extra premium on account of the impairment (substandard risks). If the data on risks accepted at the regular rate (standard) had been included along with the substandard, the mortality would probably have been lower, as they were assumed to be the best grade only.

The published experiences of life insurance companies have shown an increasing *relative* mortality with advancing age under those classified as "functional" murmurs. For organic murmurs the reverse has generally been noted. The cases classed as constant systolic apex, not transmitted, in Table I apparently contained an appreciable proportion of murmurs due to organic changes which has had its effect upon the percentages when arranged by age of the life insured. This is indicated in Table II, where classes B and C have been combined.

TABLE II

"FUNCTIONAL" HEART MURMURS—WITHOUT HYPERTROPHY. EXPERIENCE OF PRINCIPAL COMPANIES TO 1928

AGES AT DATE OF ISSUE	A—CONSTANT SYSTOLIC APEX MURMUR		B AND C—OTHER MURMURS MORE TRULY "FUNCTIONAL"	
	NUMBER OF DEATHS	EXTRA MORTALITY OVER NORMAL, %	NUMBER OF DEATHS	EXTRA MORTALITY OVER NORMAL, %
15 to 34	103	84	85	1
35 to 44	68	61	65	16
45 and over	63	22	68	68
All	234	56	218	21

It seems probable that a marked proportion of the cases in group A were murmurs due to organic lesion, although no evidence, other than the murmur, was found by the medical examiner. In the group obtained by combining B and C the mortality is distinctly above the standard or normal except at the younger ages. This is in accordance with medical expectation where the murmurs at the younger ages are frequently associated with adolescence. Opinions differ, however, with regard to the middle and older ages. Is the extra mortality due to errors in diagnosis or do some of those classified as "functional" murmurs presage organic lesions?

The insurance companies recognize that all of the five murmurs are not of equal significance. Several companies, for example, treat applicants with an inconstant systolic apex murmur and those with a constant systolic basic murmur over the pulmonary area, slightly more liberally than those with the other three types of "functional" murmurs. Perhaps when more data have accumulated, a different alignment may be found.

An investigation made this year by the New York Life Insurance Company showed an extra mortality of 39 per cent (217 deaths) in the group of constant systolic apex murmurs not transmitted, accepted as impaired risks and an appropriate additional premium charged therefor. When the material was divided into policies issued from 1915 to 1924 and those from 1925 to 1934 the company had a more favorable experience in the latter than in the former, probably due to better diagnosis. A very carefully selected group with this heart defect might have a mortality only slightly above the normal.

In dealing with a large class there are many subdivisions, reflecting the variations from the average mortality. If, for example, the extra mortality in a class of heart murmurs was 50 per cent, a subdivision into several categories might indicate an extra 25 per cent in the one-tenth most favorable cases and 75 per cent among the one-tenth least favorable.

Judging from the experience of the life insurance companies a functional murmur should not be disregarded, certainly not after middle life. The companies have a method of rating each risk, whereby differentiations are made not only by type of murmur but also by age. For example, the extra mortality might be assumed to be 10 per cent at age 30 for a person with a constant systolic apex murmur not transmitted, but 35 per cent at age 45.

An analysis of the causes of death in the collective investigation (M.I.S.) shows that there were 94 deaths from organic disease of the heart among the cases accepted at substandard rates with functional murmurs, and there would have been 23 deaths in a corresponding group of lives without that impairment. In other words, the death rate from organic heart disease was four times the normal.

*Organic Heart Murmurs.*—In the preceding section we have considered the so-called functional murmurs and shall now turn to the organic ones. I am conscious of the differences of opinion among the specialists with regard to the importance of the systolic murmur. There have been wide ranges in thought from the early days when such a murmur was considered to indicate clearly some damage to the organ, to a recent period when it was stated by certain authorities to be of minor importance. I am not so much concerned, however, with these diverse opinions as with the actual mortality results of insuring persons with the various types of murmur. In determining the condition of the heart the companies must rely on examinations made by men of widely different backgrounds, ranging from physicians with ordinary training to the highest specialists in the profession. The statistical evidence, therefore, is based on the aggregate opinion of the medical profession, and, on the average, the companies get a reasonably correct statement of the clinical condition as they select their examiners carefully. The physician in the small town or in the country district may not have the specialized training of his metropolitan brother, but he is likely to have a valuable knowledge of the applicant's habits and manner of life.

Among applicants for life insurance the most common form of heart murmur is a constant systolic apex murmur, transmitted to the left. The data were divided according to degree of enlargement of the heart (hypertrophy) but no exact definition can be given of slight or moderate hypertrophy.\*

The results of the cooperative investigation made by the principal companies is given in Table III.

TABLE III

MEDICAL IMPAIRMENT STUDY (1929)  
CONSTANT SYSTOLIC APEX MURMUR, TRANSMITTED TO LEFT

	NUMBER OF DEATHS	EXTRA MORTALITY OVER NORMAL, %
Without hypertrophy	1,231	124
With slight hypertrophy	394	134
With moderate hypertrophy	196	376

The opinion held twenty-five or more years ago that moderate hypertrophy was of little moment if properly compensated is evidently incorrect. In fact the experience of the companies seems to show that the extent of the hypertrophy indicates the degree of the valvular damage. Nature is probably trying to compensate for the leakage by increasing the thickness of the heart muscle.

\*It will be noticed from the heart chart that the medical examiner is expected to indicate the size of the heart both on the diagram and by measurements. He is also asked to state his opinion as to the degree of hypertrophy, if any. This opinion is given due weight at the home office in making the classification. In many cases further studies are made, including roentgenograms.



This phase of heart murmur is so vital that I am submitting an important contribution to the subject, based on recent statistics of the New York Life Insurance Company. The data are divided into two decennial periods according to the years in which the policies were issued. All cases were excluded where histories of rheumatism, chorea, tonsillitis, or similar infection were given.

TABLE IV  
EXPERIENCE OF THE NEW YORK LIFE TO 1935  
CONSTANT SYSTOLIC APEX MURMUR TRANSMITTED TO LEFT

WITHOUT HYPERTROPHY	NUMBER OF DEATHS	EXTRA MORTALITY OVER NORMAL, %
Policies issued 1915 to 1924	1,132	113
Policies issued 1925 to 1934	258	104
Total	1,390	111
WITH SLIGHT HYPERTROPHY		
Policies issued 1915 to 1924	222	133
Policies issued 1925 to 1934	116	227
Total	338	159
WITH MODERATE HYPERTROPHY		
Policies issued 1915 to 1924	144	227
Policies issued 1925 to 1934	53	366
Total	197	256

The evidence is convincing that a constant systolic apex murmur, transmitted to the left, is a serious impairment, with an anticipated mortality on the average of at least double the normal, if without enlargement. The *extra* mortality of the principal companies to 1928 in that class was 124 per cent and in the New York Life to 1935 it was 111 per cent, the amount of the data in both studies being too large to controvert the results. The death rate from heart diseases was far above the normal; 8, 10, and 15 times the normal in the three classes listed in Table IV. In fact, 65 per cent of the total number of deaths in the group with moderate hypertrophy was from heart affections.

With regard to slight hypertrophy, under the same kind of murmur, the extra mortality was 134 per cent in the cooperative investigation and 159 per cent in the recent research of the individual company—results which cannot be disregarded. With moderate hypertrophy the mortality is further apart but is evidence that an extra mortality of at least 250 per cent (three and one-half times the normal death rate) must be expected on the average.

Before leaving this type of heart murmur I should like to deal with a history of rheumatism associated with it. Fifty years ago such a condition was considered to be very serious and recent investigations have confirmed that early impression (Table V).

It is admitted that the companies do not get a history of infection in all cases where it has occurred, but the evidence is clear that an attack of rheumatism followed by this heart murmur is of major importance.

TABLE V

CONSTANT SYSTOLIC APEX MURMUR, TRANSMITTED TO LEFT, WITH A HISTORY OF RHEUMATISM OR CHOREA  
MEDICAL IMPAIRMENT STUDY (1929)

	NUMBER OF DEATHS	EXTRA MORTALITY OVER NORMAL, %
Without hypertrophy	307	231
With slight or moderate hypertrophy	158	322

The findings in Table V have been confirmed by the more recent experience of the New York Life. Combining the different kinds of infection—rheumatism, chorea, tonsillitis, and scarlet fever—an extra mortality was experienced under the above type of murmur of 112 per cent (289 deaths) without hypertrophy, 196 per cent (145 deaths) with slight, and 341 per cent (154 deaths) with moderate hypertrophy. Based on these findings and similar studies the companies in the aggregate provided for an extra mortality by charging suitable extra premiums.

In the joint experience of the companies, the largest group with heart murmurs was divided into two groups, depending on the nature of their occupation—the white collar class, and those in heavy manual labor—excluding occupations for which an extra charge was made. Without entering into details it may be said that there was a distinctly higher death rate among the latter than among the former, other conditions being alike. If, for example, the extra mortality was 100 per cent among the white collar class, it would be approximately 150 per cent among the heavy manual workers.

I shall now deal briefly with three more of the serious forms of heart murmurs, as revealed by our life insurance companies' records (Table VI).

TABLE VI

MEDICAL IMPAIRMENT STUDY (1929)  
WITHOUT HYPERTROPHY

TYPES OF MURMUR	NUMBER OF DEATHS	EXTRA MORTALITY OVER NORMAL, %
Constant systolic basic murmur, aortic area, transmitted upward	134	157
Constant diastolic basic murmur, aortic area, transmitted downward	34	357
Constant apex murmur, presystolic or diastolic.	41	380

The number of deaths in all but the first group is too small to give definite conclusions as to the exact mortality, but allowing a substantial margin for fluctuations the rates of extra mortality indicate the degree of hazard approximately.

*Hypertrophy Without Murmur.*—In only a small proportion of the applicants for insurance do we find hypertrophy without any kind of

a heart murmur; the companies generally provide for an extra mortality of about 50 per cent with slight, and of 75 per cent with moderate hypertrophy. This is partly based on a recent investigation which showed an extra mortality of 88 per cent (85 deaths) with slight or moderate hypertrophy.

*History of Murmur.*—What of the cases where there is a history of a murmur but none can be found now? The companies have not published anything of moment in this line but their practice reflects the point of view of their medical directors and actuaries. The day has passed when a murmur, apparently organic, heard by a reliable examiner in recent years is entirely disregarded in valuing the risk. Time and again a man dies of heart disease a year or two after the most careful examination, including electrocardiogram and roentgenogram, had failed to disclose any defect, yet there was a history of such a finding at an earlier examination. In this I refer not to difference of opinion with regard to the character of the murmur but to the presence of the murmur itself. I leave the answer to the heart specialists. Was the report of a murmur as organic a year ago by a reliable examiner which is not apparent now, an error of diagnosis or what was the fact?

*Heart Murmur With a History of Other Impairments.*—The question may probably be asked:—Have the companies any reliable information regarding mortality where there is a murmur with a *history* of rapid pulse, high blood pressure, albuminuria, or glycosuria, not now found? The answer is that the result of such a study was published in 1934 which proved that a history of these impairments added decidedly to the hazard. Although not found at the time of examination a weakness is indicated which makes the persons in this class less able to stand the effect of the heart murmur, and a return of the rapid pulse, albuminuria, and the other diseases is more likely than their occurrence among persons who have never had these defects.

*Heart Murmur With Overweight.*—At one time the opinion was freely expressed among physicians that overweight was a serious addition to a heart murmur. It may not be generally known that marked overweight in itself is a distinct impairment. For example, among persons who are 35 per cent overweight and insure at age 40 the companies provide for an extra mortality of 45 per cent and for those at age 50, of 55 per cent. No conclusive statistical evidence has yet been brought forward to show the mortality among those who combine marked overweight with a heart murmur. The companies are inclined to assume that the extra mortality is the sum of those arising from the respective impairments.

*Factors in Connection With Murmurs.*—I am not unmindful that there are many more factors to take into account than those already

mentioned—such as the habits of life, and the strength of the inhibitions. The clinician is primarily interested in the individual and the actuary in the group of lives, after the individuals are classified by the medical profession. In consulting with his patient the physician tries to bring out all factors favorable or unfavorable to recovery or to prolonging life. This means almost an infinite variety of types, which the actuary would find it necessary to consolidate into a comparatively few groups so as to get a sufficient number of persons in each to justify his conclusions.

To avoid misunderstanding it should be mentioned that the mortality ratios in this article do not necessarily represent the death rate among those who present themselves to heart specialists. On the one hand the specialist sees many in poor health who would not be accepted by the insurance companies and on the other there is a twofold selection involved in connection with applicants for insurance (a) by the company in determining what risks should be accepted and on what terms and (b) by the applicant who decides whether or not it is to his interest to accept the policy. The interplay of these two factors (a) and (b) may lead to results which are difficult to interpret. On the whole, however, it may be said that the mortality indicated in the insurance companies' investigations would approximately represent the additional death rate among those with the impairments in question, provided they were otherwise in good health and had no other major impairments.

*Clinical Records.*—The actuary has given the results of his researches to the world and is most desirous of comparing them with those of the heart specialist. The difficulties of the latter are great. He is not always a methodical man who keeps his records in first class shape for research. He is naturally more interested in keeping his clients in health than in collaborating with a statistician. The principal difficulty, however, lies in his inability to keep track of his patients, to determine whether they are living, and if not, the dates of death. He may see many of them only once on consultation, while those in clinics too frequently disappear from observation. It is hoped that these obstacles will be overcome in a measure in the case of clinical records, through cooperation with an actuary whose experience with mortality problems has been extensive. A comparison of studies based on the records of clinicians and on those of insurance companies may prove to be of great value.

## Appendix

### *Instructions for Examination of the Circulatory System*

It is suggested that, following examination of the heart when quiet, the applicant be requested to bend over, touching the floor six or eight times. This will bring out many murmurs that otherwise would be missed.

*Transmission of Murmur.*—Indicate by arrow on heart chart whether it is transmitted to axilla or back, or both, in the case of apical murmur; or to vessels of neck, or across sternum to the opposite side in basic murmurs. If a poorly defined murmur is discovered, note findings with applicant in recumbent position; also with breath held with chest completely inflated and deflated. Observe effect of inspiration on murmur. Be on the lookout for any dyspnoea, cyanosis or marked and prolonged overaction of heart with failure to return to normal after three minutes' rest.

*Cardiac Hypertrophy.*—Determine if this condition exists by percussion with applicant erect in addition to noting point of maximum intensity of the apical beat. If the outer heart border reaches slightly beyond the nipple line, record moderate hypertrophy; if well within the nipple line, none. Record a little hypertrophy only after careful examination and when quite certain the outer border lies between these two points.

*History of Acute Infectious Disease.*—Give exact month and year of any acute rheumatic fever, tonsillitis or any other infection or acute illness which may have been an etiological factor.

*Blood Pressure Observations.*—In order to remove any psychic element the blood pressure should not be taken when the applicant is obviously nervous or apprehensive. It is advisable to distract the applicant's attention from the procedure by conversation. If the systolic pressure is found to be abnormally high, or the diastolic over 100, repeat the observation at the close of the examination. Be sure there is no faulty adjustment of the cuff of the apparatus and the arm is not hyperextended, which may partially destroy the apposition of the brachial artery to the cuff. Note any increase of the pulse pressure. A slight increase is frequently noted in mitral regurgitation and aortic obstruction, a decided increase in aortic regurgitation. With such a finding further auscultation of the heart sounds is indicated. Be sure to specify at which phase the diastolic pressure is recorded.

*Character and Rate of Pulse.*—Be sure that any pulse rate over 88 is not due to psychic disturbance and make a later observation. If pulse is persistently rapid, look for goiter or pulmonary signs or elevated temperature. Count the number of irregularities or intermissions over a whole minute. If pulse is irregular or intermittent, exercise applicant and report if abnormality increases or disappears. Note if the pulse be high tension, dirotic or Corrigan types or weak and thready in character. Make the diagnosis of myocarditis with great caution and only in the presence of the usually accepted signs—extreme irregularity or intermittency, pulsus alternans, weak and distant heart sounds, low blood pressure, etc.

# HEMODYNAMIC STUDIES IN EXPERIMENTAL CORONARY OCCLUSION\*

## III. DENERVATED HEART EXPERIMENTS

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IN TWO preceding reports,<sup>1, 2</sup> we demonstrated that ligation of the left anterior descending coronary branch in dogs was followed by an immediate decrease in cardiac output without any corresponding diminution in circulating blood volume. The absence of this diminution in blood volume ruled out the possibility that there was any direct loss of blood or plasma in or about the injured myocardium of sufficient magnitude to account for the decrease in cardiac output.<sup>3, 4</sup> It also precluded the possibility that a toxic substance, such as histamine, was liberated from the injured myocardium in sufficient quantities to trap the circulating blood in the peripheral capillary bed and thus diminish minute volume.<sup>5</sup> The possibility remained, however, that nervous reflexes from the heart to the peripheral blood vessels and to the heart might affect the cardiac output.

In these studies, therefore, we employed a procedure with the object of interrupting all the motor and sensory impulses to and from the heart respectively. This involved resection of both thoracic sympathetic chains from stellate through sixth or seventh thoracic ganglia, as well as bilateral sympatheticovagotomy in the neck. The aortic depressor nerves were severed with the vagosympathetics, whereas the nerves from the carotid sinuses were left intact. Although White<sup>6</sup> considers them to be of no importance even if they exist, possible sensory pathways via the cardiac nerves and cervical sympathetic ganglia and thence directly into the cervical spinal cord would, according to Braeucker<sup>7</sup> and Heinbecker,<sup>8</sup> still be left intact by these procedures. With these reservations in mind, then, we were dealing with a denervated heart.

The prevalent immediate cause of death after the final as well as the preliminary procedures was pneumonia. Seventy-five per cent of the total number of animals initially subjected to operation died before the final experiments could be performed. In the remaining 25 per cent, two groups with ten dogs in each, the following procedures were successfully carried out. Under nembutal anesthesia, the right chest was opened in the fourth interspace. The right lung was compressed anteriorly and mesially with packs which were held in place

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Aided by grants from the Lucius N. Littauer and Walter W. Naumburg Funds.

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Aided by a grant from the Emanuel Libman Fellowship Fund.

by lung retractors. The sympathetic chain, thus exposed, was resected from the sixth or seventh thoracic ganglion up to and including the stellate. The packs were then removed and the chest closed in the usual way. One week later the left chest was opened in the fourth interspace under anesthesia. The sympathetic chain was exposed as before, and resected from the sixth or seventh thoracic ganglion up to and including the stellate. The packs were then removed and in one group of ten dogs, the double carrick bend was placed around the left anterior descending coronary branch in the manner described in the preceding report.<sup>2</sup> In the other group of ten dogs (controls), the knot was placed around relatively avascular left ventricular muscle. The chest was then closed in the usual manner. One week later the animals were again anesthetized. Both vagosympathetic trunks in the neck were severed, following which the physiological studies were carried out in series as described in our first report.<sup>1</sup> The left anterior descending coronary branch or some left ventricular muscle, in the two groups, respectively, was then ligated from the exterior of the chest and the studies repeated. Electrocardiograms were taken before and after the various steps in the procedure. None of the animals survived the bilateral sympatheticovagotomy for more than twenty-four hours. Complete autopsies were done on all the animals which succumbed.

#### PRELIMINARY OBSERVATIONS

Following the right sympathectomy, there was an appreciable retardation in pulse rate. The electrocardiographic changes\* were similar to those found with an increase in right vagal tone.<sup>9</sup> This apparent increase in vagal tone was probably only relative to the decrease in opposing sympathetic tone.<sup>10</sup> At the end of a week these changes became less marked.

After left sympathectomy, there was usually a further slowing of the heart rate although this was not invariable. The electrocardiographic changes were now similar to those with an increase in left vagal tone.<sup>9</sup> In several cases heart-block developed and was usually fatal. In the others, the manifestations of relatively increased vagal tone tended to subside during the course of a week.

After bilateral sympatheticovagotomy in the neck, several changes took place. The respirations became slower and irregular in depth. This made the determination of the ether circulation time more difficult and therefore less reliable. There was no irregularity, however, in the rate of oxygen consumption and hence no difficulty from this source in the estimation of the cardiac output. The temperature tended to fall somewhat more than in previous experiments.<sup>1, 2</sup> The cause for this greater fall was obscure. It might have been due in

\*To be reported in detail in a separate communication.

part to denervation of the lungs, which in the dog are very important in the regulation of temperature.<sup>11</sup> The arterial blood pressure was now subject to only minimal fluctuations in contrast to its lability in our previous experiments. There was occasionally a slight increase in heart rate after both vagosympathetic trunks were severed. Except for this occasional change in rate, the electrocardiogram was now relatively normal. The intravenous injection of sodium cyanide had a paradoxical effect.<sup>12</sup> Whereas the injection was followed in previous experiments by a retardation in heart rate and electrocardiographic evidence of increased vagal tone, in these animals with denervated hearts there was an acceleration.

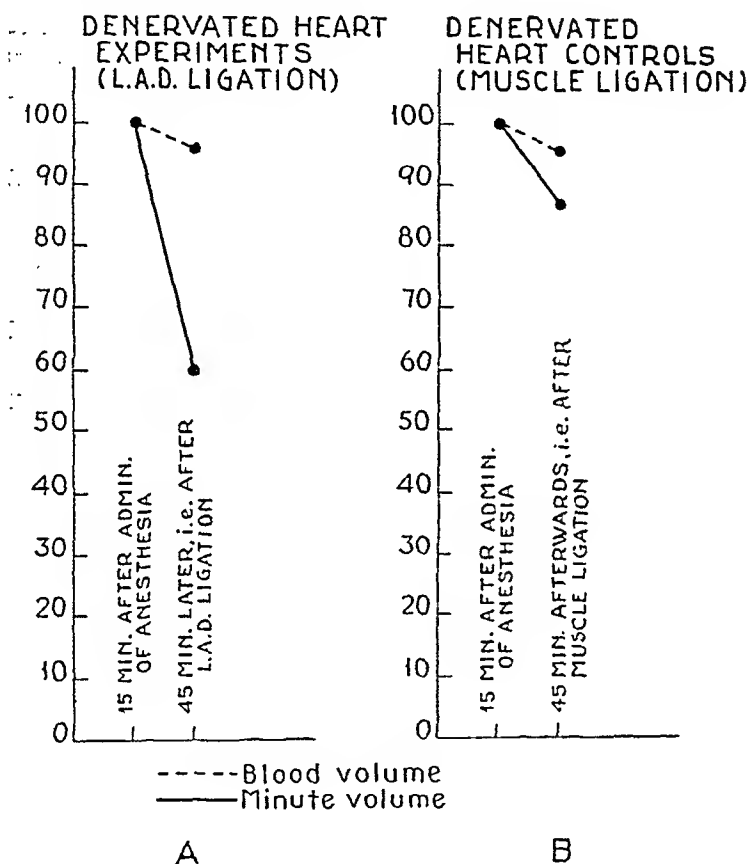


Fig. 1.—Average per cent changes in cardiac output and in blood volume per square meter of surface area.

#### RESULTS IN FINAL EXPERIMENTS

The effect of ligation of ventricular muscle on the cardiac output (Table I) was not appreciably different from that observed in all the control studies done in previous experiments.<sup>1, 2</sup> There was a moderate immediate decrease in average minute volume (Fig. 1B).

The effect of ligation of the left anterior descending coronary branch in these animals (Table II) was not significantly different from the effect of ligation in previous experiments.<sup>1, 2</sup> The immediate decrease in average cardiac output was definitely more profound than in the control group (Fig. 1A). In the graph demonstrating the individual case



TABLE I  
DENERVATED HEART CONTROL EXPERIMENTS

DOG NO. AND SEX	DATES OF OPERATIVE PROCEDURES			TIME OF TESTING	WEIGHT IN KG.	TEMPERATURE (F.)	PULSE RATE PER MINUTE	OXYGEN CONSUMPTION IN C.C. PER MINUTE	ARTERIOVENOUS OXYGEN DIFFERENCE, VOLUMES PER CENT	CARDIAC OUTPUT MINUTE VOLUME PER SQ. METER IN C.C.	TOTAL BLOOD VOLUME PER SQ. METER IN C.C.	HEMOGLOBIN PER CENT	TOTAL SERUM PROTEINS—GRAMS PER CENT	BLOOD PRESSURE			CIRCULATION TIME		REMARKS
	RIGHT SYMPATHECTOMY (71-6)	LEFT SYMPATHECTOMY (71-6) LIGATURE PLACED AROUND MYO. FIBERS	BILATERAL VAGOTOMY AND LIGATION											ARTERIAL IN MM. OF MERCURY	VENOUS IN CM. OF WATER	ETHER IN SEC.	CYANIDE IN SEC.		
74F	9/21/36	10/1	10/8	Preligation* Postligation	14.4 14.4	101.4 100.0	130 136	118.0 112.0	5.23 6.55	3394 2572	2086 1948	57 58	6.36 6.06	148 150	0 0	5.0 5.5	8.5 9.0	10/9 Dog died. Autopsy: Left chest wound gangrenous; atelectatic pneumonia of both lungs; thread torn through muscle; L.A.D. patent; no infarct.	
76F	9/21	10/1	10/10	Preligation Postligation	7.0 7.0	97.0 96.0	102 100	66.0 63.0	3.81 4.08	4223 3765	2073 1935	51 58	5.49 5.77	118 110	0 0	4.5 4.0	12.5 13.5	10/11 Dog died. Autopsy: Atelectasis of both lungs; muscle ligated; L.A.D. patent; no infarct.	
303G	10/22	10/29	11/5	Preligation Postligation	13.0 13.0	100.6 100.3	116 111	115.0 115.0	3.22 3.80	5765 4880	2583 2364	55 63	5.55 5.23	113 105	3.5 2.5	6.5 6.5	17.7 13.5	11/6 Dog died. Autopsy: Lungs congested; muscle ligated; L.A.D. patent; no infarct.	
77F	•Ligation of left ventricular muscle																		

\*Ligation of left ventricular muscle.

TABLE I—CONT'D

46G ♂	10/30	11/ 6	11/12	Preligation Postligation	6.6 6.6	97.5 94.7	148 134	69.5 73.0	2.67 3.13	6605 5920	2158 2064	53 57	6.34 6.39	135 110	1.0 0	3.5 4.0	8.0 9.0	11/13 Dog died. Bilateral bronchopneumonia; muscle torn through by thread; L.A.D. patent; no infarct.
84G ♂	11/14	11/21	11/28	Preligation Postligation	17.5 17.5	99.6 97.0	110 110	112.0 108.0	3.89 5.68	3810 2514	2220 2098	67 67	5.53 6.02	143 148	2.5 2.3	7.5 6.5	14.0 12.0	11/28 Dog killed. Muscle ligated; L.A.D. patent; no infarct.
94G ♂	11/16	11/27	12/ 3	Preligation Postligation	15.8 15.8	97.0 95.8	108 104	163.0 148.0	3.32 4.43	6950 4736	2286 2183	53 53	6.47 6.49	130 140	0 0	8.5 10.0	15.0 14.0	12/3 Dog killed. Muscle ligated; L.A.D. patent; no infarct.
99G ♂	11/17	11/27	12/ 4	Preligation Postligation	23.0 23.0	102.3 101.2	124 124	183.0 173.0	3.85 3.93	5240 4860	3298 3258	62 65	6.15 6.28	145 145	4.5 5.5	4.5 4.5	13.0 11.0	12/4 Dog killed. Muscle ligated; L.A.D. patent; no infarct.
3H ♀	11/18	11/30	12/ 7	Preligation Postligation	10.8 10.8	98.0 95.0	120 112	103.0 99.0	3.31 2.26	5938 7960	2755 2496	63 67	5.82 5.72	133 130	1.5 2.0	7.5 6.0	12.0 10.0	12/8 Dog died. Bilateral hemorrhagic pleural effusion; lungs atelectatic; scattered pneumonic patches; muscle ligated; L.A.D. patent; no infarct.
23H ♀	11/25	12/ 2	12/10	Preligation Postligation	8.8 8.8	99.6 97.4	154 130	91.0 87.0	2.98 4.43	6383 4100	2320 2508	70 73	4.19 4.17	118 105	0 3.4	6.5 ?	14.0 indef.	12/10 Dog died. Muscle ligated; L.A.D. patent; no infarct.
12H ♂	11/24	12/ 1	12/ 8	Preligation Postligation	15.8 15.8	100.0 100.0	128 114	116.5 105.0	3.96 3.41	4165 4360	2660 2535	71 71	5.51 5.64	105 105	1.5 1.5	5.5 6.0	15.0 13.0	12/8 Dog killed. Muscle ligated; L.A.D. patent; no infarct.

TABLE II  
DENERVATED HEART EXPERIMENTS

DOG NO. AND SEX	DATES OF OPERATIVE PROCEDURES				TIME OF TESTING	WEIGHT IN KG.	TEMPERATURE (F.)	PULSE RATE PER MINUTE	OXYGEN CONSUMPTION IN C.C. PER MINUTE	ARTERIOVENOUS OXYGEN DIFFERENCE, VOLUMES PER CENT	CARDIAC OUTPUT MINUTE VOLUME PER SQ. METER IN C.C.	TOTAL BLOOD VOLUME PER SQ. METER IN C.C.	HEMOGLOBIN PER CENT	TOTAL SERUM PROTEINS—GRAMS PER CENT	ARTERIAL IN MM. OF MERCURY	VENOUS IN CM. OF WATER	CIRCULATION TIME		REMARKS
	RIGHT SYMPATHECTOMY (71-6)	LEFT SYMPATHECTOMY (71-6)	AROUND L.A.D.	BILATERAL VAGOTOMY AND LIGATION													ETHER IN SEC.	CYANIDE IN SEC.	
187 ♂	8/18/36	8/29		9/ 4	Preligation* Postligation	12.0 12.0	99.0 98.6	120 120	113.0 75.0	3.46 4.18	5558 3050	2520 2280	85 85	3.67 4.14	140 130	1.5 1.0	4.0 5.0	9.0 9.0	9/5 Dog died. Autopsy: Patchy bilateral bronchopneumonia; L.A.D. not patent; incipient infarct of indefinite extent.
301 ♂	8/21	8/31		9/16	Preligation Postligation	12.5 12.5	100.2 98.0	122 108	88.0 93.0	3.25 5.07	4500 3044	1952 1880	76 77	5.06 4.49	120 108	1.0 1.5	5.0 5.0	13.0 15.0	9/17 Dog died. Autopsy: Lungs congested; L.A.D. not patent; infarct present.
401 ♂	8/23	9/ 4		9/17	Preligation Postligation	9.6 9.6	101.4 100.8	136 130	88.0 90.0	3.73 5.28	4640 3357	1989 1995	58 62	4.03 3.87	125 95	1.5 2.0	5.5 8.0?	13.0 17.5	9/18 Dog died. Autopsy: Old pericardial adhesions; L.A.D. not patent; incipient infarct of indefinite extent.

\*Ligation of left anterior descending coronary branch.

TABLE II—CONT'D

64F ♂	9/18	9/26	10/ 5	Preligation Postligation	16.6 16.6	101.8 -	150 134	163.0 138.5	1.96 <sup>9</sup> 5.03	11370 <sup>9</sup> 3770	2940 2620	63 69	4.71 4.95	125 90	2.0 2.0	5.5 --	10.5 ---	10/5 Dog died of ventricular fibrillation. Autopsy: L.A.D. not patent; no ap-parent infarct.
68F ♂	9/19	9/29	10/ 6	Preligation Postligation	9.0 9.0	99.1 98.3	114 114	92.0 131.0	2.51 7.03	7550 3846	2284 2134	60 67	6.59 6.51	150 140	2.5 5.0	7.5 11.0	11.0 13.0	10/7 Dog died. Autopsy: L.A.D. not patent; incipient infarct.
71F ♀	9/19	9/30	10/ 7	Preligation Postligation	12.7 12.7	99.0 98.0	106 108	119.0 110.0	3.88 5.40	5040 3340	2576 2455	50 54	6.23 6.01	112 90	2.0 4.0	4.0 5.0	9.0 15.0	10/8 Dog died. Autopsy: Lungs congested; L.A.D. not patent; incipient infarct of indefinite extent.
4G ♀	10/10	10/20	10/26	Preligation Postligation	10.6 10.6	99.8 96.6	122 118	100.0 79.0	2.20 3.92	8390 3710	1897 1835	69 70	5.70 5.96	115 115	0.5 2.0	11.0 <sup>9</sup> 5.5	10.0 <sup>9</sup> 21.5 <sup>9</sup>	10/27 Dog died. Autopsy: L.A.D. not patent; infarct present.
18G ♀	10/17	10/28	11/ 4	Preligation Postligation	16.0 16.0	101.6 101.8	138 132	140.0 135.5	3.53 5.37	5570 3548	4200 <sup>9</sup> 3836 <sup>9</sup>	93 93	5.64 5.55	122 122	1.0 0	3.5 4.5	11.0 <sup>9</sup> 11.5	11/5 Dog died. Autopsy: Pneumonic patches in both lungs; L.A.D. not patent; infarct present.
22G ♀	10/17	11/ 2	11/10	Preligation Postligation	13.0 13.0	99.8 99.6	150 158	111.5 97.0	5.80 6.38	3110 2452	2274 2446	71 71	5.87 5.70	160 120	5.5 0	8.5 <sup>9</sup> 5.5	11.0 9.5	11/11 Dog died. Autopsy: L.A.D. not patent; incipient infarct of indefinite extent.
62G ♂	11/ 9	11/16	11/20	Preligation Postligation	17.0 17.0	101.2 101.0	136 128	168.0 129.0	7.39 8.51	3058 2040	2662 2645	98 88	5.28 5.37	145 145	0.5 2.5	-- 4.0	13.0 16.0	11/21 Dog died. Autopsy: Lungs congested and atelectatic; L.A.D. not patent; infarct present.

distribution with reference to immediate change in cardiac output (Fig. 2), there is evidence that the diminution in minute volume was consistent.

In contrast to previous experiments<sup>1, 2</sup> there was usually an immediate decrease in the arterial blood pressure following ligation of the vessel as against minimal changes in the control group. The ether and cyanide circulation times in both groups tended to be somewhat more prolonged than those reported previously. Contrary to our former experience, the average fall in temperature was greater in the control group than in the vessel ligation group. In view of the variable factor introduced by sympatheticovagotomy, it is impossible to evaluate

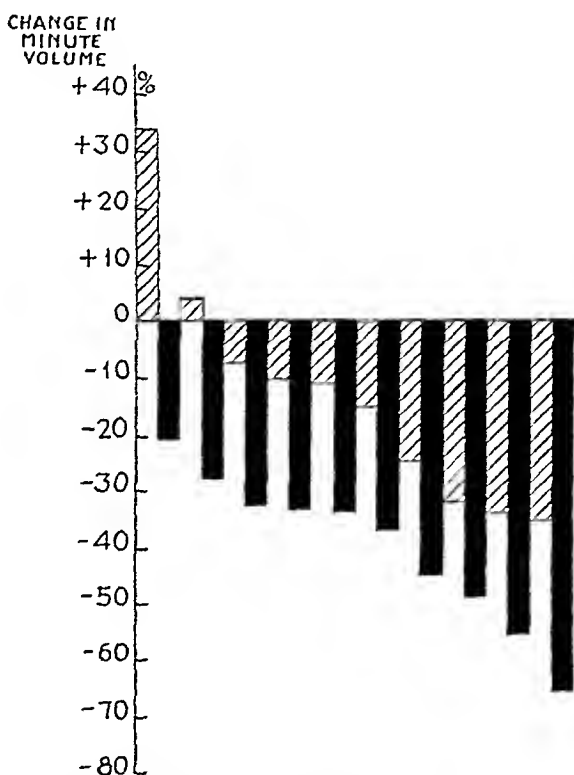


Fig. 2.—Individual case distribution with reference to the changes in cardiac output directly after the procedure.

this finding. Ligation of the artery was followed by the same characteristic electrocardiographic alterations previously observed,<sup>13</sup> namely, an elevation of the R-T transition in Lead I with or without an S-T depression in Lead III. Ventricular fibrillation was occasionally observed. These changes were never seen in any of the control experiments.

In other respects there were no essential differences between the findings in these experiments and those in the experiments in which the heart had not been denervated.<sup>1, 2</sup> The cyanide circulation time tended to be prolonged after ligation of the vessel, whereas the ether circulation time remained relatively unchanged. The blood volume

was usually slightly diminished in both the ligation and the control groups, and the erythrocyte count and the hemoglobin percentage together with the cell volume were usually slightly increased in both groups. The venous pressure was variable, and there were no significant changes in pulse rate or in serum proteins.

#### DISCUSSION

In these experiments all or most of the motor and sensory pathways to and from the heart respectively were interrupted. There was, nevertheless, a definite decrease in cardiac output without any corresponding change in blood volume following left anterior descending coronary branch ligation. The reduction in output could not, therefore, have been caused by reflexes from the injured myocardium to visceral or peripheral blood vessels or to the heart.

The immediate fall in blood pressure following vessel ligation in these experiments might in part be attributed to the absence of the masking effect of the usually wide fluctuations in vasomotor tone hitherto observed.<sup>1, 2</sup> Another probable factor was the interruption of some of the nervous pathways for compensatory vasoconstriction. That some vasoconstriction took place, however, is attested to by the fact that in most instances the decrease in cardiac output was proportionately greater than the fall in blood pressure.

It may be argued that occlusion of the left anterior descending coronary branch primarily caused only a slight cardiogenic diminution in minute volume, that this initiated a compensatory reflex vasoconstriction via the carotid sinus,<sup>14, 15</sup> and that this vasoconstriction was responsible for a great part of the observed decrease in cardiac output by impeding the venous return to the heart. Inasmuch as the carotid sinus and other possible vasomotor mechanisms<sup>14</sup> were left intact in our experiments, it is impossible to refute this argument conclusively. There are, however, considerations which weaken the force of such a contention. It is known, for example, that neither experimental<sup>17</sup> nor clinical<sup>18</sup> hypertension, presumably associated with a generalized vasoconstriction, diminishes the cardiac output. It is therefore likely that such vasoconstriction as probably occurred in our experiments did not diminish the venous return to the heart and hence played no predominant part in the significant decrease in cardiac output observed.

It is evident, therefore, that the diminution in cardiac output following left anterior descending coronary branch occlusion in the dog is largely, if not entirely, primarily cardiogenic. In other words, it is attributable to the inability of the left ventricle to expel all the blood it receives. As a result of this, there is an accumulation of blood in the pulmonary veins and capillaries. We are dealing, then, in these experiments with (1) cardiogenic hypokinetic circulatory failure and (2) left ventricular congestive failure.

## SUMMARY

1. A technic is described for ligation of the left anterior descending coronary branch in the dog after denervation of the heart.
2. The changes following ligation of the vessel consist of a fall in cardiac output and blood pressure and a prolongation of the cyanide circulation time.
3. The hypothesis that the decrease in minute volume is neurogenic is considered, with some reservations, unsubstantiated.
4. The preponderance of evidence supports the theory that the decrease in cardiac output is cardiogenic.
5. The ligation of the left anterior descending coronary branch in the dog is followed by cardiogenic hypokinetic circulatory failure and left ventricular congestive failure.

## REFERENCES

1. Gross, Louis, Mendlowitz, M., and Schauer, G.: Hemodynamic Studies in Experimental Coronary Occlusion: I. Open Chest Experiments, *AM. HEART J.* 13: 647, 1937.
2. Mendlowitz, M., Schauer, G., and Gross, Louis: Hemodynamic Studies in Experimental Coronary Occlusion: II. Closed Chest Experiments, *AM. HEART J.* 13: 664, 1937.
3. Keith, N. M.: Blood Volume Changes in Wound Shock and Primary Hemorrhage, Great Britain: Medical Research Committee: Report of the Special Investigation Committee on Surgical Shock and Allied Conditions, No. 9, March, 1919.
4. Blalock, A.: Acute Circulatory Failure as Exemplified by Shock and Hemorrhage, *Surg. Gynec. Obst.* 58: 551, 1934.
5. Eppinger, H., and Schürmeyer, A.: Ueber den Kollaps und Analoge Zustände, *Klin. Wehnsehr.* 7: 777, 1928.
6. White, J. C.: The Autonomic Nervous System, New York, 1935, The Macmillan Co., page 40.
7. Braeueker, W.: Die Fortschritte und die Zukunft der Sympathicuschirurgie, *Nervenarzt.* 6: 449, 1933.
8. Heinbecker, P.: Anatomie and Physiologic Criteria for Surgical Relief of Cardiac Pain, *J. Thoracic Surg.* 2: 517, 1933.
9. Cohn, A. E.: On the Difference in the Effects of Stimulation of the Two Vagus Nerves on the Rate and Conduction of the Dog's Heart, *J. Exper. Med.* 16: 732, 1912.
10. Rothberger, C. J., and Winterberg, H.: Ueber die Beziehungen der Herznerven zur Form des Electrocardiogramms, *Arch. f. d. Ges. Physiol.* 135: 559, 1910.
11. Richet, C. R.: *La chaleur animale*, Paris, 1889, Felix Alean, pp. 258-301.
12. Mendlowitz, M., and Schauer, G.: A Paradoxical Reaction of the Rate of the Denervated Heart and the Blood Pressure to the Intravenous Injection of a Small Dose of Sodium Cyanide in the Dog. (In manuscript.)
13. Gross, Louis, and Calef, Benson: Electrocardiographie Changes in the Dog Following Sudden Occlusion of the Left Anterior Descending Coronary Branch Under Various Experimental Conditions. (In manuscript.)
14. Siciliano, L.: Les effets de la compression des carotides sur la pression, sur le coeur et sur la respiration, *Arch. Ital. de Biologie* 33: 338, 1900.
15. Hering, H. E.: Die Karotissinus reflexe auf Herz und Gefässe, Dresden and Leipzig, 1927, Theodor Steinkopff.
16. Heymans, C., Bouckaert, J. J., Farber, S., and Hsu, F. Y.: Spinal Vasomotor Reflexes Associated With Variations in Blood Pressure, *Am. J. Physiol.* 117: 619, 1936.
17. Tigerstedt, R. A. A.: *Die Physiologie des Kreislaufes*, Berlin u. Leipzig, 1922, Walter de Gruyter and Co., Vol. 3, pp. 62-122.
18. Gladstone, S. A.: *Cardiac Output and Arterial Hypertension*, New York, 1935 (privately published).

# THE ELECTROCARDIOGRAPHIC CHANGES IN ACUTE PERICARDITIS

## A CLINICAL AND PATHOLOGICAL STUDY\*

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THE diagnosis of acute pericarditis, especially of the purulent type, is often difficult. The frequency with which this condition is found post mortem, when clinically unsuspected, is well known. For several years, it has been recognized that patients with acute pericarditis, with and without effusion, and with hemopericardium, may show electrocardiographic changes of the RS-T segments and T-waves. The cause of these abnormalities has not been finally determined. The literature contains few reports of patients with acute pericarditis in which serial electrocardiograms were taken and in which complete pathological studies were done.

Schwab and Herrmann<sup>1</sup> reviewed the literature and reported seven cases of acute pericarditis. Although minor changes occurred in the electrocardiograms of all, only two cases showed significant elevations of the RS-T segments. In one of these, acute purulent pericarditis was present at autopsy, but a microscopic description of the myocardium was not given. No other post-mortem examinations were available. They felt that the positive deviations in the RS-T segments were caused by myocardial ischemia produced by the rise of intrapericardial pressure resulting from effusion. In one of the cases, however, a rapid tamponade from hemopericardium produced no alteration of the RS-T segments.

Scott, Feil, and Katz<sup>2</sup> differentiated the electrocardiographic changes of pericardial effusion from those of myocardial infarction and suggested that the electrocardiogram might be of diagnostic value in pericardial effusion. In a case of hemopericardium and in one of acute purulent pericarditis, elevated R-T segments returned to normal without drainage of the pericardial sac.

In a well-studied case of pneumococcic pericarditis, in which paracentesis and pericardiotomy were done, Harvey and Scott<sup>3</sup> reported elevation of the R-T segments in all leads, with return to normal before death. This return to normal was attributed to drainage of the pericardium. At autopsy "no coronary disease or gross myocardial damage was found."

In a patient with purulent pericarditis reported by Purks,<sup>4</sup> an electrocardiogram the day before death showed elevated R-T segments in

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Leads I and II. At post-mortem examination a large pericardial effusion was associated with acute pericarditis and subjacent myocarditis.

Master, Romanoff, and Jaffe<sup>5</sup> studied 52 cases of pneumonia with daily electrocardiograms. In one case a marked elevation of the R-T segments was present in all leads on the day of death. This was the only case which showed pericarditis at autopsy. Foci of degeneration were found in the muscle fibers but no mention was made of the microscopic appearance of the pericardium or subjacent myocardium.

Koucky and Milles<sup>6</sup> recently reviewed the literature on stab wounds of the heart in which surgical repair was successful and serial electrocardiograms were obtained. They reported an additional case of stab wound of the anterior surface of the right ventricle in which recovery followed suture of the ventricle. Purulent pericarditis was proved on the fourth postoperative day and open drainage was instituted. Electrocardiograms on the first, fifth, and ninth days after operation revealed elevated R-T segments of about equal height in Leads I and II. In Lead III the R-T segment was normal or only slightly elevated.

In a patient with a stab wound involving the anterior descending branch of the left coronary artery, Elkin and Phillips<sup>7</sup> obtained electrocardiograms before, during, and after operation. A pericardial friction rub was present from the third to the sixth days. A teleroentgenogram on the fourth day showed evidence of pericardial effusion. The record taken before operation, during a period of extreme cardiac tamponade, was practically normal. Ten minutes after operation, slight elevation of the R-T segments was present in Lead I and slight depression in Lead III. Thirty-six hours after operation, the R-T segments were elevated in all leads but especially in Lead II. These changes persisted for several days with gradual return to normal.

In two cases of stab wounds of the heart involving the anterior surface of the left and right ventricles, respectively, Porter and Bigger<sup>8</sup> obtained frequent electrocardiograms. The tracing obtained fourteen hours after operation in Case 1 resembled that seen after anterior myocardial infarction. The records on the fourth and fifth days, however, showed elevated R-T segments in all leads, particularly in Lead II. In the second case, elevation of the R-T segments was present in all leads and again, after the second day, was most marked in Lead II. Pericarditis was not suspected clinically in either of these cases.

Barnes<sup>9</sup> analyzed the findings in seven patients with acute coronary occlusion in which the electrocardiograms were characterized by elevation of the R-T segments in the three limb leads. Because the usual reciprocal deviation of the RS-T segments in Leads I and III was lacking, localization of the infarct was difficult. From clinical and post-mortem studies, he concluded that electrocardiograms of this type after coronary occlusion were the result of a coincident pericarditis.

In a subsequent article, however, Wolferth and Wood<sup>10</sup> reported 10 cases with similar electrocardiograms. They ascribed this type of record to infarction involving both the anterior and posterior surfaces of the left ventricle. Post-mortem studies in two cases showed this lesion in both. No mention was made of the presence or absence of pericarditis. These authors logically explained this type of electrocardiogram as the summation effect of both anterior and posterior infarction.

Experimental studies in this field have been largely concerned with the production of electrocardiographic changes by increasing the intrapericardial pressure. Katz, Feil, and Scott<sup>11</sup> injected saline and oil into the pericardial sac of dogs. In some instances, the R-T segments were elevated in all leads. On release of pressure, the electrocardiograms returned to normal. These changes were thought to be the result of myocardial anoxemia. Herrmann and Schwab,<sup>12</sup> by increasing the intrapericardial pressure of goats, reduced the pulse pressure to minimal levels. In some animals, the R-T segments were elevated in four leads of the electrocardiogram. Diminished circulation to the posterior as well as to the anterior surface of the heart was advanced as the cause of the changes. As controls in studies of coronary ligation on dogs, Barnes and Mann<sup>13</sup> opened the pericardium and manipulated the heart without ligation of vessels. On the fourth and fifth days thereafter, elevation of the R-T segments occurred in two of three animals. Fowler, Rathe, and Smith<sup>14</sup> noted similar electrocardiographic changes in dogs when the pericardium was merely opened. Microscopically, inflammation of the epicardium extended into the adjacent myocardium. Degenerative changes were evident in the superficial muscle fibers. Pericardial adhesions were numerous. The authors attributed the electrocardiographic changes to myocardial damage.

In an effort to determine the cause of the electrocardiographic changes found in acute diseases of the pericardium, we have studied a variety of conditions in which acute pericarditis may occur. Serial electrocardiograms were taken in 63 patients with pneumonia or empyema. In this group there were 23 deaths and 18 autopsies. Five of these patients had acute pericarditis. Three cases of pericarditis secondary to uremia with two post-mortem examinations were likewise studied. In three patients with rheumatic pericarditis, no autopsies were obtained. Autopsies were obtained in three more cases of acute pericarditis. One of these was probably gonococcic; another followed a stab wound of the right auricle; and the last was a hemopericardium from a ruptured aorta. Six of the entire group had definite and similar changes in the electrocardiograms, and all were proved post mortem to have pericarditis. Two cases of uremia and two of pneumonia, with pericarditis at autopsy, had no such electrocardiographic changes. In all of the post-mortem studies numerous sections from

both auricles and ventricles were examined microscopically. We are reporting clinical and pathological studies on the six cases with "positive" electrocardiograms.

CASE 1.—(No. 38958.) B. E., a colored housewife, thirty-five years of age, was admitted to Medical Service A on Aug. 18, 1935. She complained of pains in the joints. The family and past medical histories were not significant except for an ectopic pregnancy in 1929. The patient dated her illness to February, 1935, when she noted pains in the knees, ankles, and wrists. She was up and about for three months, with little improvement. Persistent fever was noted after May. On August 5, the swelling of the joints became worse and the fever higher. During the illness, she lost 25 pounds in weight.

Examination revealed an emaciated, feverish, and "toxic" woman. Motion of both ankles and the right shoulder, wrist, and knee was extremely painful. The lungs were clear. A systolic murmur was heard at the apex of the heart. The rhythm was regular and the rate 120. A purulent urethral discharge was present and marked tenderness existed in the right adnexal region. Right femoral phlebitis was also noted. With rest in bed, the arthritic symptoms became less severe, but the temperature remained elevated. On October 29, however, the fever was high and peritonitis spreading from the pelvis was thought to be present. The arthritis was reactivated. X-ray studies of several joints showed destructive changes suggestive of gonorrheal arthritis. In December, marked bilateral cervical lymphadenopathy occurred which subsided after x-ray treatments.

Following a gynecological examination on Jan. 23, 1936, the temperature rose sharply, generalized abdominal pains were present, and the arthritis was aggravated. Continuing for several days, a pericardial friction rub was first heard on January 24. Because of a marked pulsus paradoxus on February 2, the pericardial sac was tapped through the fifth intercostal space in the anterior axillary line and 280 c.c. of yellow pus were aspirated. The specific gravity of this fluid was 1.020 and there were 19,350 cells, mostly polymorphonuclear neutrophils, per cubic millimeter. Two days later, 450 c.c. of purulent exudate were again removed. No bacteria were demonstrated in either specimen on smear and culture. Inoculation of guinea pigs was negative for tuberculosis. The cardiac signs disappeared. The fever continued to be septic in type. Large bedsores occurred, and the patient died on March 13, 1936.

Of a large amount of laboratory data, the significant findings were two strongly positive gonococcus complement fixation tests, secondary anemia, normal leucocyte counts, with a shift to the left in the polymorphonuclear neutrophils, and repeatedly negative blood cultures. Blood Wassermann and Kahn tests were negative. For electrocardiograms, see Fig. 1.

*Autopsy* (No. 5507).—The autopsy was done seven hours after death. Anatomical Diagnosis: Primary cause of death undetermined. History of former pelvic operation. Scar in lower abdomen. Absence of right fallopian tube and ovary. Fibrous adhesions between abdominal scar and stump of right broad ligament. Scarring of left fallopian tube. History of polyarthritis. Chronic adhesive pericarditis. Lobular pneumonia. Fibrous pleural adhesions of lower lobes of both lungs. Fibrous adhesions between capsule of liver and peritoneal surface of diaphragm. Fatty changes of liver. Focal necroses of liver. Acute splenic tumor. Calcification of renal tubules. Hyperplasia of bone marrow. Decubitus ulcers of right hip and lower back. Small scars of right side of neck. Calcified and caseous lymph nodes.

*Pericardium and Heart*.—Dense fibrous adhesions were present between the outer surface of the pericardium and the adjacent pleurae. Except in a few small areas over the ventricles, the pericardium and epicardium were firmly united by dense

fibrous adhesions. The heart and pericardium weighed 280 gm. The myocardium was pale, but showed no focal lesions. The endocardium, valves, and coronary arteries were not remarkable.

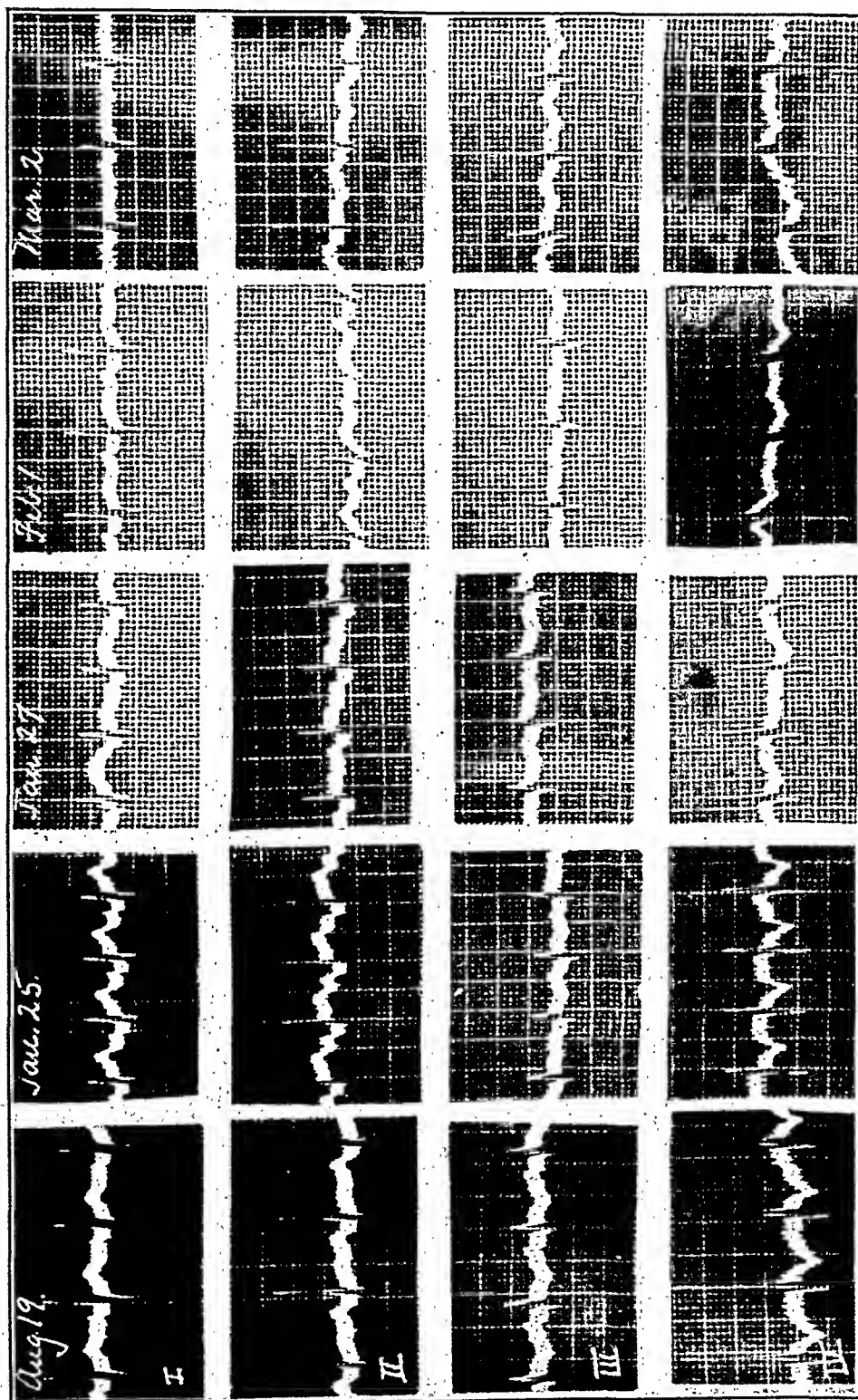


Fig. 1.—Case 1. Acute gonorrheal (?) pericarditis. The first record was taken the day after hospital admission for acute arthritis. On January 24 precordial pain and a pericardial friction rub were noted. In the record of January 25 note the elevation of the R-T segment in Leads I, II, and III, greatest in Lead II. There is a gradual return toward normal as pericardial exudate accumulated (Feb. 1). On February 2 and 4 the pericardial sac was aspirated and considerable pus obtained. Some residual T-wave changes are seen in Leads I and II of the last record. A relatively deep Q-wave is seen in Lead III in some of the records. There is no essential change in the chest lead (Lead IV), taken with the precordial electrode at the apex area and the indifferent electrode on the left leg.

\*Photographs by Mr. Emil Forney.

Microscopically, much of the fatty tissue of the pericardium and epicardium was replaced by scars, and the adhesions were also composed of hyaline fibrous tissue. Rarely were young capillaries and fibroblasts seen. Where adhesions were lacking, a little fibrin and a few round cells were present on the surface of the epicardium. In most areas scar tissue was in contact with the surface of the myocardium. Small

numbers of lymphocytes and plasma cells were present in the deeper layers of the epicardium, but none were seen among the muscle fibers and there was no interstitial scarring of the myocardium (Fig. 2). In many localities of both auricles and ventricles, however, the surface of the myocardium was exceptionally irregular as if groups of fibers had disappeared. No evidence of rheumatic inflammation or other abnormalities was seen in the heart.

*Bacterial Studies.*—No bacteria were demonstrated in the sections of lungs and no acid-fast bacilli or other organisms were seen in the liver or caseous mesenteric lymph nodes.

CASE 2.—(No. 40853.) L. D., a white man, forty-one years old, was admitted to Medical Service B on March 14, 1936. He complained of cough and generalized pain in the abdomen. He had had previous attacks of pneumonia in 1922 and

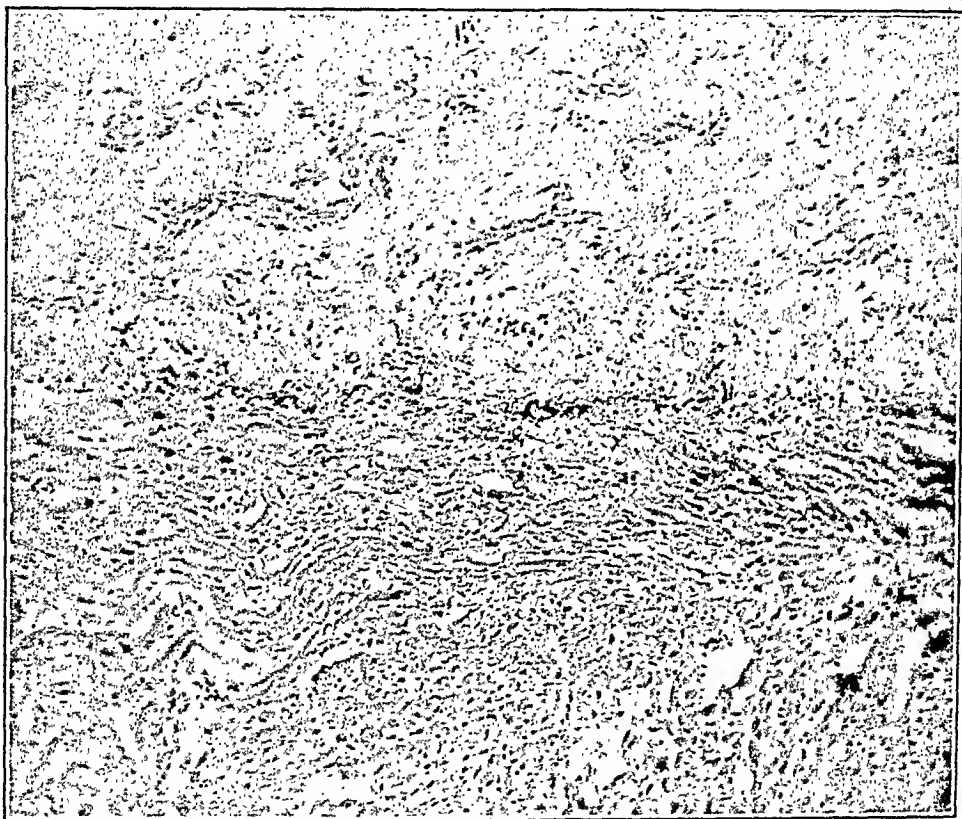


Fig. 2.—Case 1. Section of the left ventricle showing dense, fibrous, epicardial adhesions. No cellular infiltration of the myocardium is present.

1931. A cough, becoming worse four days before admission, had been present for several months. Chilly sensations were recently noted and sweating was frequent.

On admission, he was acutely ill, with rapid respirations. The right lung was clear but crackling râles were heard over the left axilla and the left infrascapular area. The heart was not remarkable. The abdomen was distended and the epigastrium tender. After some improvement, the temperature rose suddenly to 105° F. on March 19 and the temperature curve continued to be septic in type. Signs of increased pulmonary involvement were noted bilaterally, followed by evidence of fluid at the left base and axilla. On March 23, thoracentesis in the left axilla was unsuccessful. Because of pulsus paradoxus, an attempt was made to tap the pericardium. Through the fifth intercostal space in the anterior axillary line, 625 c.c. of creamy pus were removed. (Autopsy showed this pus to have come from an empyema and not from the pericardial cavity.) Death occurred March 24.

Pertinent laboratory data included cultures of hemolytic streptococci from the sputum and pleural exudate. A blood culture was sterile. The leucocyte count rose from 5,250 on admission to 19,400 on March 22. Blood Wassermann and Kahn tests were negative. For electrocardiograms, see Fig. 3.

*Autopsy* (No. 5515).—The autopsy was done fifty-seven hours after death. Anatomical Diagnosis: Lobular pneumonia and multiple abscesses of left lung. Septicemia—hemolytic streptococcus. Extensive edema and hemorrhages of both lungs. Fibrinopurulent exudate of left pleural cavity, pericardium, and epicardium—hemolytic streptococcus. Foci of subepicardial myocarditis. Small hemorrhages in spleen, lymph nodes, adrenals, and brain. Acute splenic tumor. Hyperplasia of lymph nodes, splenic tumor type. Hyperplasia of bone marrow. Acute glossitis. Scarring of pancreas and testes. Chronic prostatitis.

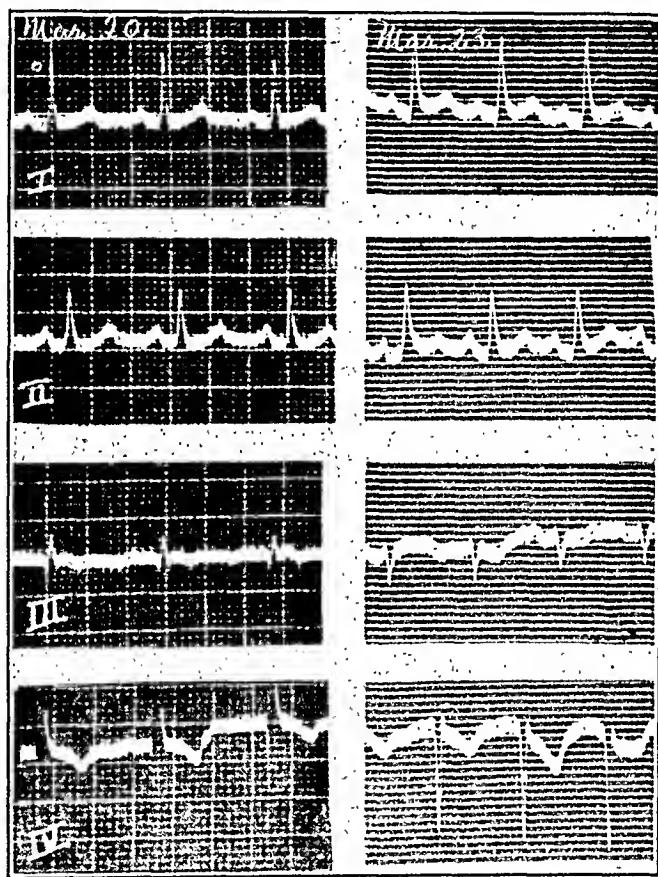


Fig. 3.—Case 2. Lobular pneumonia with empyema and early pericarditis (hemolytic streptococcus). The record of March 20, is not abnormal. That of March 23 shows an elevation of the R-T segments in Leads I and II, with slurring of the descending limb of the R-wave. A slight change in the axis deviation is apparent. No essential change is present in the chest lead.

*Lungs*.—Numerous small, soft, gray areas were scattered through both lobes of the left lung. These lesions, microscopically, were small abscesses surrounded by zones of lobular pneumonia. In both lungs were extensive areas of edema and hemorrhage and in the left pleural cavity were 250 c.c. of fibrinopurulent exudate.

*Pericardium and Heart*.—A thin layer of fibrinopurulent exudate on the outer surface of the pericardium was continuous with the pleural exudate. Only a thin layer of fibrin was present on the inner surface of the pericardium and on the epicardium, associated with not more than 40 c.c. of cloudy pericardial fluid. The heart weighed 310 gm. and, on section, the left ventricle was slightly dilated. The endocardium, valves, and coronary arteries showed no gross lesions.



Microscopically, a fibrinopurulent exudate was on the outer surface of the pericardium. Only small amounts of fibrin were present on the epicardium and on the inner surface of the pericardium, but both the pericardium and epicardium were heavily infiltrated with polymorphonuclear neutrophiles, lymphocytes, and mononuclear phagocytes. Where there was little epicardial fat; small numbers of polymorphonuclear neutrophiles, lymphocytes, and plasma cells were scattered about the superficial blood vessels and among the superficial muscle fibers of the myocardium (Fig. 4). In the sections from both auricles and ventricles, a few of the muscle fibers were necrotic. The deeper portions of the myocardium showed no microscopic lesions.

**Bacterial Studies.**—In post-mortem cultures of the blood from the heart and the pleural exudate, hemolytic streptococci and colon bacilli were grown. *Streptococcus viridans* and a colon bacillus were cultured from the left lung. With bacterial stains,



Fig. 4.—Case 2. Section of the left ventricle. The myocardium is invaded by the purulent epicardial exudate. The superficial muscle fibers are degenerating.

large numbers of gram-positive cocci in chains were seen in the pleural exudate and on both surfaces of the pericardium, but no organisms were found in the myocardium. Many gram-positive cocci were, likewise, present in the exudate of the left lung.

**CASE 3.**—(No. 39636.) T. A., a colored man, thirty-five years of age, was admitted to Medical Service A on Oct. 30, 1935, with a chief complaint of pain in the chest. He had had no serious illnesses and the family history was irrelevant. A cough had been present for several days, and following exposure to rain, he had had sharp pain of pleuritic type in the left lower chest. The cough was worse and shortness of breath was marked.

He was acutely ill on examination and perspired freely. Respirations were rapid and shallow. Signs of consolidation were present over the lower lobe of the left lung. The heart showed no abnormalities. The abdomen was distended and tender in the

left upper quadrant. Delirium was constant and the temperature remained at about 102° F. A marked pulsus paradoxus was noted on November 4, and he died on November 5.

Cultures of the sputum showed pneumococcus Type III, and a blood culture was positive for the same organism. The leucocyte count rose from 4,350 on November 1 to 28,000 on November 4. Blood Wassermann and Kahn tests were negative. For electrocardiograms, see Fig. 5.

*Autopsy* (No. 5390).—The autopsy was performed thirteen hours after death. Anatomical Diagnosis: Confluent lobular pneumonia of left lung, pneumococcus Type III. Extensive fibrinopurulent exudate in both pleural cavities. Patchy areas of atelectasis and edema of lungs. Marked fibrinopurulent exudate, with beginning organization, of pericardium and epicardium. Foci of acute subepicardial myo-

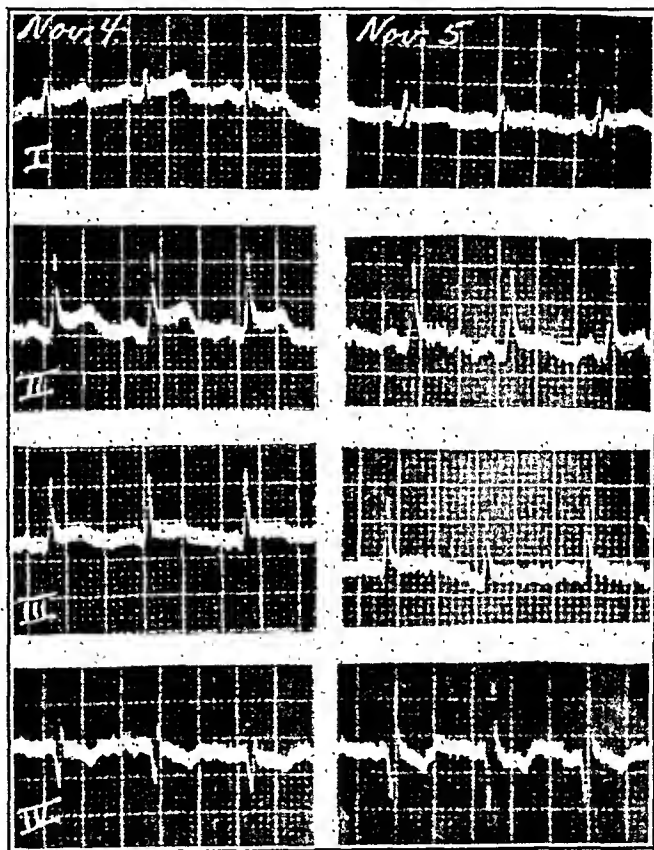


Fig. 5.—Case 3. Lobar pneumonia with bilateral empyema and fibrinopurulent pericarditis (pneumococcus). Note the elevation of the R-T segments in Leads I, II, and III of the electrocardiograms with no significant change in the chest lead.

carditis. Hyperplasia of peribronchial lymph nodes. Enlargement of axillary lymph nodes. Acute diaphragmitis. Hemorrhages in splenic pulp. Focal necroses in liver. Fatty changes of liver, slight. Small abscess in one kidney. Hyperplasia of bone marrow. Distention of stomach and intestines.

*Lungs*.—Confluent areas of gray consolidation, typical of pneumonia microscopically, were present in both lobes of the left lung. On the pleural surfaces of both lungs was a thick fibrinopurulent exudate. The left pleural cavity contained 500 c.c., and the right, 400 c.c. of cloudy fluid. The pleural exudate was continuous with a similar exudate on the external surface of the pericardium.

*Pericardium and Heart*.—The pericardium was thickened and indurated. A fibrinopurulent exudate was present on the internal surface and on the epicardium. About 400 c.c. of cloudy fluid were found in the pericardial sac. The heart with the



epicardial exudate weighed 410 gm. In many localities, for a distance of 2 or 3 mm. beneath the epicardium, the heart muscle was pale. The heart showed no other gross lesions.

*Microscopically*, the cells of the exudate on the pericardium and epicardium were predominantly polymorphonuclear neutrophils many of which were necrotic. Both the pericardium and epicardium were edematous and heavily infiltrated with polymorphonuclear neutrophils, mononuclear phagocytes, lymphocytes, and plasma cells. The small blood vessels were engorged and, in many areas, the fat was necrotic. In some localities, organization was occurring. Except where the epicardial fat was thick, the cellular infiltration reached the surface of the myocardium and extended into it for short distances about the blood vessels and superficial muscle fibers, which were pale-staining and frayed. Many of the nuclei of these fibers were pyknotic or vacuolated. Numerous small hemorrhages were present in the stroma. The deeper layers of the myocardium were normal in appearance.

*Bacterial Studies.*—At autopsy, blood culture from the heart showed numerous colon bacilli. *Pneumococcus* Type III was grown from the left lung. Large numbers of gram-positive cocci were stained in sections of the exudate from the lung, pleurae, pericardium, and epicardium. No organisms were seen in the myocardium.

CASE 4.—(No. 40463.) J. A., a colored male, fifty-seven years of age, was admitted to Medical Service B on Feb. 1, 1936. He complained of pain in the chest and left shoulder and shortness of breath. The family and past medical histories were not significant. He had been in good health until January 27, when he noted malaise and anorexia. He remained at home for three days, but returned to work on January 30, when he was seized with pain in the chest and cough productive of rusty sputum.

On admission he was acutely ill and respirations were rapid and shallow. The right middle and lower lobes were thought to be consolidated. The heart was enlarged to the left and the sounds were faint. The cardiac rate was 132, and the rhythm was totally irregular. A pulse deficit was noted. The abdomen was moderately distended. The left shoulder was swollen and painful on motion. The patient continued very ill, with a temperature sustained at 103° F. The cardiac rhythm was regular on February 2. A pericardial friction rub was present on February 4 and 5. On February 8 death occurred.

Significant laboratory data were as follows: *pneumococcus* Group IV was cultured from the sputum. On February 3, blood culture showed 100 colonies per c.c. of *pneumococcus* Group IV. On February 5, venous blood pressure was 8.8 cm. of water. Blood Wassermann and Kahn tests were negative. For electrocardiograms, see Fig. 6.

*Autopsy* (No. 5465).—The autopsy was done two hours after death. Anatomical Diagnosis: Lobar pneumonia of right lung. Septicemia, *pneumococcus* Group IV. Organizing fibrinopurulent exudate of right pleural cavity, pericardium, and epicardium, *pneumococcus* Group IV. Foci of acute subepicardial myocarditis. Acute phlegmonous abscess of left shoulder region. Swelling of left knee. Acute purulent meningitis, *pneumococcus*. Acute splenic tumor. Marked distention of intestines. Emphysema of lungs. Old fibrous pleural adhesions of left lung. Hypertrophy of left ventricle of heart. Hypertrophy of prostate. Extracapsular hyperplasia of cortical cells of both adrenals. Invasion of posterior lobe of hypophysis by basophile and chromophobe cells.

*Body and Lungs.*—The left shoulder was swollen and indurated and a deep phlegmonous abscess was found beneath the pectoral muscles in the axilla. A similar area of swelling about the left knee was not dissected. Scattered diffusely through the right lung were numerous small patches of lobular pneumonia. A thick fibrino-

purulent exudate, involving the pericardium, covered the pleural surface of the right lung and 350 c.c. of cloudy fluid were present in the pleural cavity. The left pleural sac was completely obliterated by dense old fibrous adhesions.

*Pericardium and Heart.*—The pericardium was thickened, gray, and opaque. On both the internal and external surfaces and on the epicardium was a fibrinopurulent exudate approximately 0.5 cm. in thickness. About 40 c.c. of cloudy fluid were present in the pericardial sac. The heart and epicardial exudate weighed 460 gm. On section, where there was little epicardial fat, the myocardium was pale for two or three mm. beneath the surface. The wall of the left ventricle was moderately thickened. No other gross abnormalities were noted.

*Microscopically,* the exudate on the surfaces of the pericardium and epicardium was composed of fibrin and disintegrating polymorphonuclear neutrophils, into

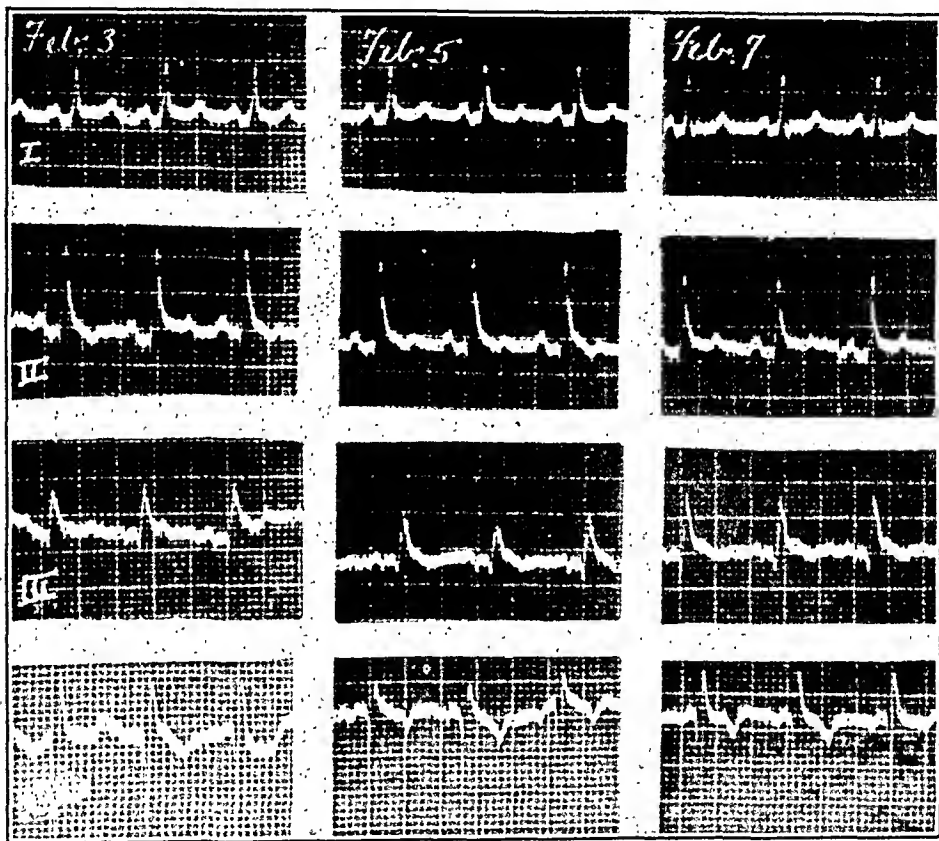


Fig. 6.—Case 4. Lobar pneumonia with empyema (right) and fibrinopurulent pericarditis (pneumococcus Type IV). Pericardial friction rub noted February 4. Death February 8. The first electrocardiogram shows an elevation of the R-T segments in Leads I, II and III, with slurring of the descending limb of the R-wave. The changes are greater in Leads II and III but no significant Q pattern is present. Return of the R-T segment to normal is seen in Lead I. The chest lead shows only slight R-T segment elevation in the record of February 5.

which fibroblasts and capillaries were growing. The pericardium and epicardium were heavily infiltrated with these cells and abscesses in the fatty tissue were numerous. Except where the epicardial fat was thick, the purulent exudate extended to the surface of the myocardium and moderate numbers of polymorphonuclear neutrophils and round cells were present among the superficial muscle fibers (Fig. 7). Many of these fibers, particularly in the right ventricle, were pale-staining and the fibrils were broken or absent. Most of the nuclei were vacuolated (Fig. 8). A few of the most superficial fibers were necrotic. In the deeper layers of the myocardium, no such changes were present. The muscle fibers of the left ventricle were diffusely hypertrophied.

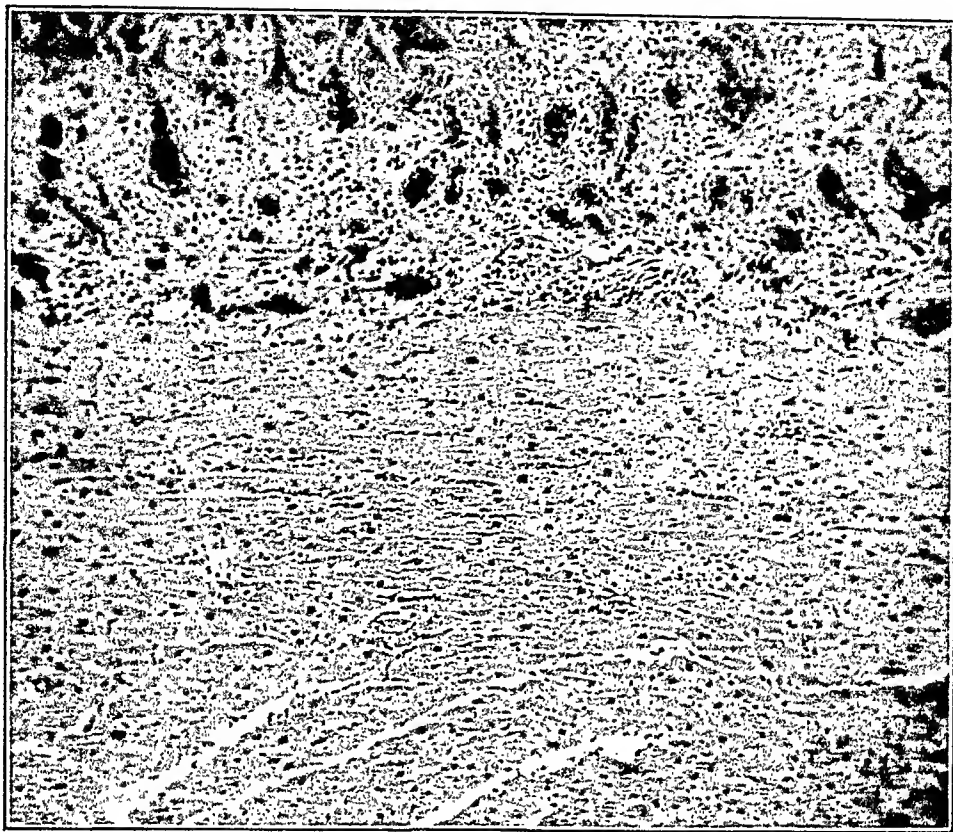


Fig. 7.—Case 4. Section of the left ventricle. The epicardial exudate is organizing. Leucocytes are scattered among the muscle fibers.

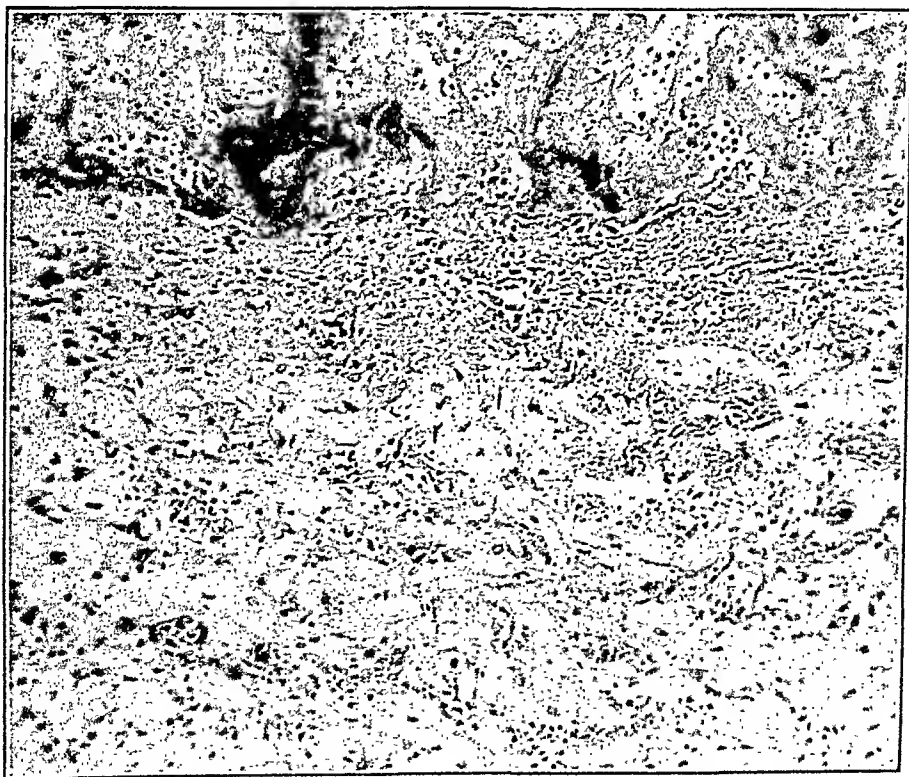


Fig. 8.—Case 4. Section of the right ventricle. The fibrinopurulent epicardial exudate is apparent. Leucocytic infiltration and degeneration of the myocardium is striking.

*Bacterial Studies.*—Pneumococcus Type IV was grown at autopsy in pure culture from the pericardial cavity. From the right lung only a bacillus of the colon group was cultured. In sections, occasional gram-positive cocci were seen in the pericardial and epicardial exudate, but none were found in the myocardium. Similar organisms were stained in the meningeal exudate. No bacteria were demonstrated in the pleural exudate, in the areas of pneumonia, or in the exudate of the left axilla.

CASE 5.—(No. 40278.) J. K., a white boy of eighteen years, was admitted to Surgical Service A on Jan. 13, 1936. He was in a critical condition from a stab wound in the third intercostal space 5 cm. to the left of the sternum. The pulse rate and blood pressure could not be determined and the heart sounds were inaudible. After emergency treatment for shock, the heart sounds were heard at a rate of 140 per minute. Less than two hours after admission, the patient was operated on by Dr. John B. Flick. The pericardium was tense and distended with blood.

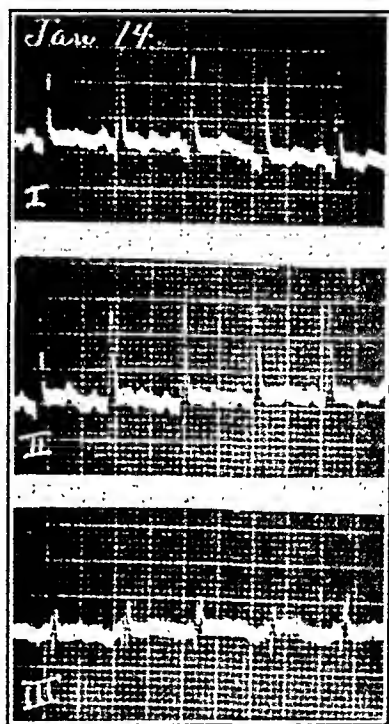


Fig. 9.—Case 5. Stab wound of right auricle. Death thirty-six hours after operation. Acute fibrinous pericarditis and lobular pneumonia. The electrocardiogram was taken about fifteen hours after operation. Note the elevation of the R-T segments in Leads I and II, with some slurring of the descending limb of the R-wave.

A laceration in the right auricle just above the auriculoventricular junction was sutured. During the operation the heart stopped beating, but contractions were resumed after massage of the ventricles. A transfusion of 1,100 c.c. was given on the operating table. After operation the blood pressure rose to 138/70.

The following day there was a fever of 102° F., considerable cyanosis, and a productive cough. The respirations were 48 per minute. The heart rate was 148 and the blood pressure 114/80. A definite pulsus paradoxus was noted. Dullness was present to percussion at the bases of both lungs, with crepitant râles on the right and bronchial breath sounds at the left infrascapular area. Because electrocardiographic changes were present and a bedside x-ray plate suggested enlargement of the cardiac shadow, paracentesis was attempted, but no blood or purulent fluid could be aspirated from the pericardial sac. The temperature, pulse, and respirations continued to rise and he died thirty-six hours after operation. For electrocardiogram, see Fig. 9.

*Surgical Specimen* (No. 22771).—The autopsy was performed on the day of death by a coroner's physician. Only a few blocks of tissue were allowed for study.

*Heart*.—A thick fibrinous exudate covered the epicardium and inner surface of the pericardium, but little fluid was said to be present in the pericardial sac. The sutured laceration in the right auricle was intact, but on the endocardial aspect of this lesion was a large mural thrombus. *Microscopically*, fragments of suture material were present in the right auricle and, on either side of the laceration, the myocardium was heavily infiltrated with polymorphonuclear leucocytes. Fragments of necrotic thrombus were attached to the endocardium. On the surface of the epicardium was a thick fibrinopurulent exudate. At some distance from the laceration, the entire wall of the right auricle was also infiltrated with polymorphonuclear neutrophils, lymphocytes, and plasma cells. The muscle fibers were shrunken and the nuclei were pyknotic. In two sections of the left ventricle the epicardial fat

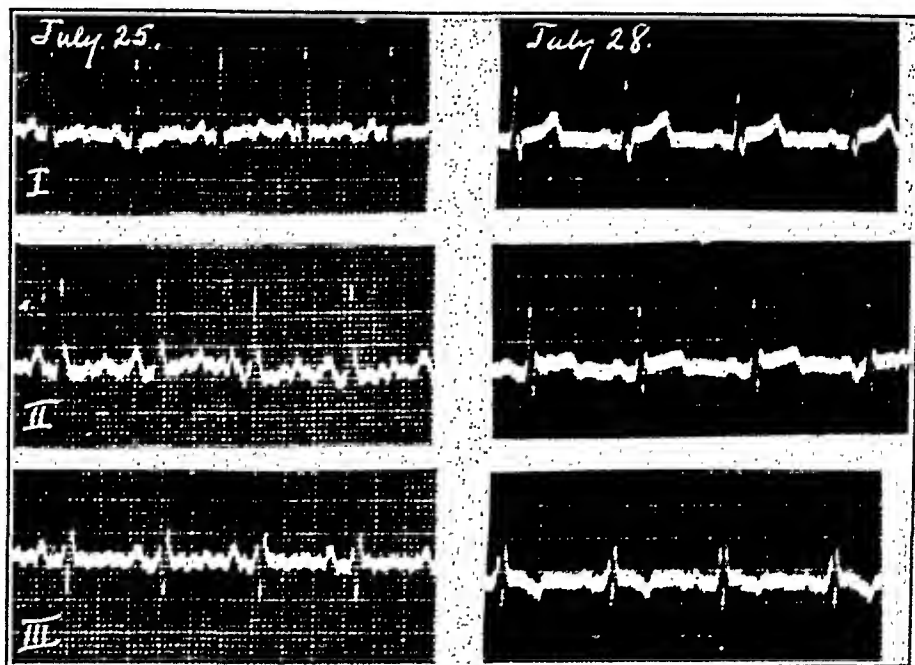


Fig. 10.—Case 6. Colored male aged forty-one years. Syphilitic aortitis with rupture into the pericardial sac. The first record was taken a few hours after admission because of agonizing chest pain and shock. It shows little of significance and no R-T segment change. The second record was taken about one hour before death. There is a slight but definite elevation of the R-T segments in Leads I and II, with inversion of the T-waves in Lead III.

was thick and the exudate did not reach the surface of the myocardium. The muscle fibers appeared normal. No other blocks were available. Large numbers of gram-positive cocci, resembling staphylococci, were stained in the exudate of the epicardium and auricular myocardium.

CASE 6.—(No. 3594.) C. J., a colored male, forty-one years of age, was admitted to Medical Service A on July 24, 1931. He had been in good health until the evening of admission when he noted nausea and oppression in the chest. He became dizzy and lost consciousness. On recovery a few minutes later, he had agonizing pain in the chest, made worse by inspiration. He was rushed to the hospital and on arrival was in shock. The blood pressure was 90/60 and the pulse 130. He vomited repeatedly. Scattered fine and coarse râles were present over the lungs. The heart showed slight enlargement to the left but no murmurs or friction rub were heard.

The abdomen was not remarkable and the right leg had been amputated below the knee. A large chronic ulcer was present over the medial aspect of the left leg.

The following day an aortic diastolic murmur was heard and the lungs were clear. On July 27 enlargement of the cardiac dullness was noted on percussion, but the patient seemed generally improved. Death occurred suddenly on July 28 after an attack of acute dyspnea with rapid disappearance of the pulse.

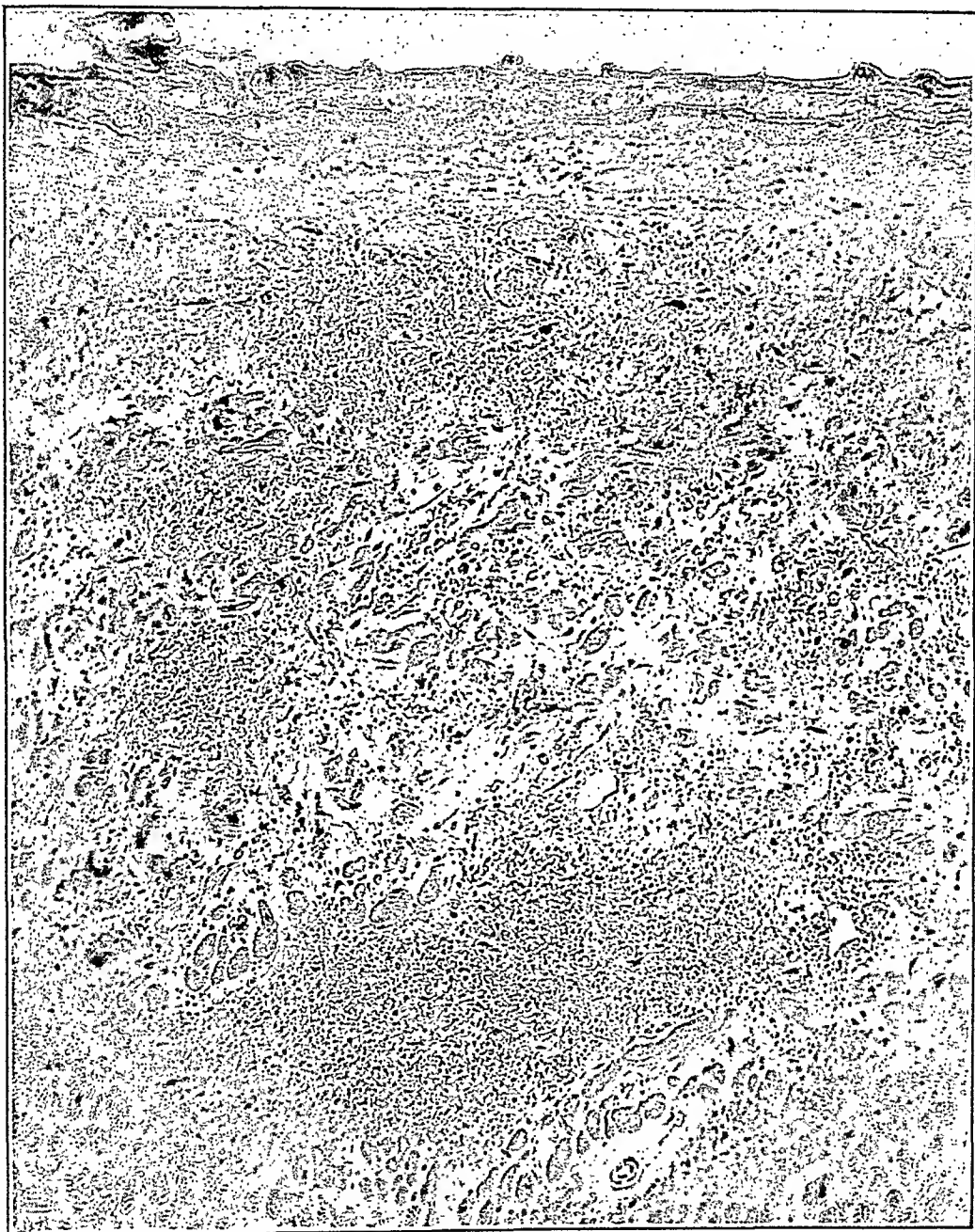


Fig. 11.—Case 6. Section of the right ventricle. The fibrinous epicardial exudate is scant. The hemorrhage and edema in the myocardium are marked. Many of the muscle fibers are degenerating or necrotic.

Laboratory data included strongly positive Wassermann and Kahn tests and slight leucocytosis. For electrocardiograms, see Fig. 10.

*Autopsy* (No. 4424).—The autopsy was done two and one-half hours after death. Anatomical Diagnosis: Syphilitic aortitis. Laceration of ascending arch of aorta with rupture into pericardial sac. Hemopericardium. Edema and hemorrhage of



pericardium. Acute fibrinous pericarditis. Foci of acute inflammation, hemorrhage, and edema in right ventricle of heart. Hypertrophy and dilatation of heart. Diffuse scarring of interventricular septum. Old tuberculous lesions in apex of right lung. Anthracosis, slight. Chronic ulcer of left leg. Absence of right leg below the knee.

*Aorta.*—Just above the ring of the aortic valve was a stellate laceration of the intima and media. Blood had extravasated through the adventitia into the pericardial cavity. In all portions of the arch, elevated fibrous plaques were present in the intima and the media beneath was grossly scarred. Microscopically, the lesions were typical of syphilitic aortitis. At the point of rupture, a large, fresh area of necrosis, associated with round cell infiltration, extended through the entire thickness of the media.

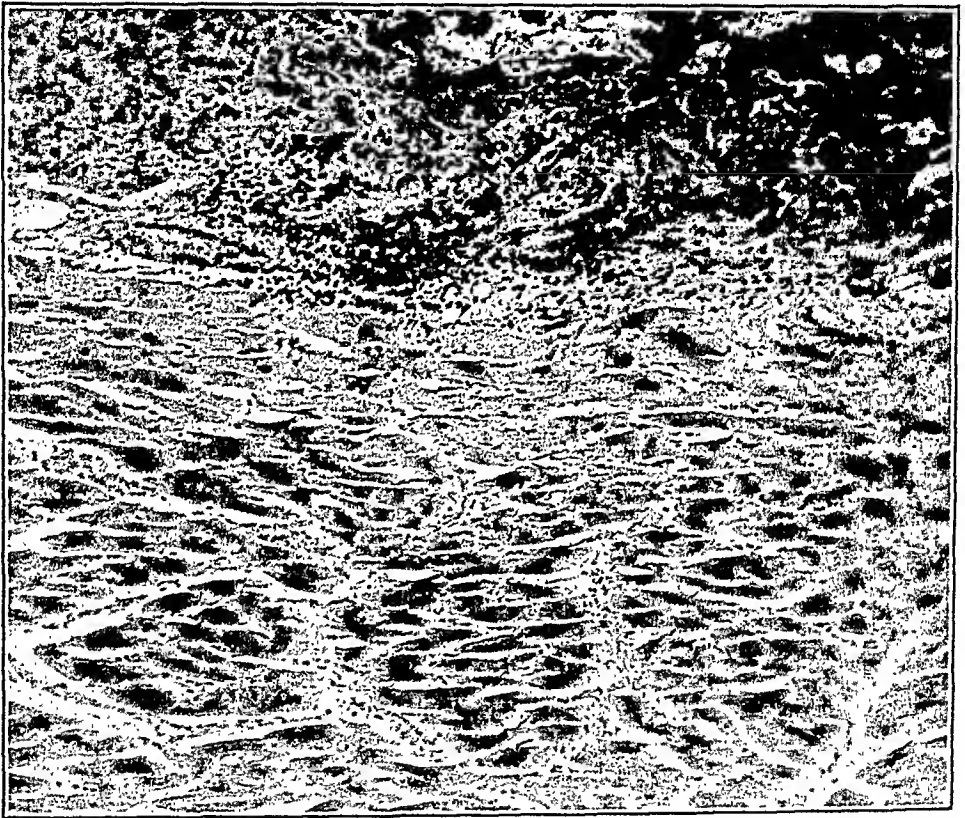


Fig. 12.—Section of the left ventricle from a case of uremic pericarditis. The epicardial exudate, composed largely of round cells, does not infiltrate the myocardium. The muscle fibers are hypertrophied.

*Pericardium and Heart.*—The anterior layer of pericardium was moist and bloody. The pericardial sac contained 750 c.c. of clotted blood. Thin layers of fibrin covered the epicardium and inner surface of the pericardium. The heart weighed 600 gm. The left ventricle particularly was hypertrophied and the wall measured 22 mm. in thickness. Small, firm, white streaks were visible beneath the endocardium in the interventricular septum. The endocardium, valves, and coronary arteries showed no lesions.

*Microscopically,* much of the fatty tissue in the pericardium was destroyed by fresh hemorrhage and edema. On the epicardium was a thin fibrinous exudate. In the areolar tissue were numerous hemorrhages and small collections of lymphocytes and plasma cells. Extravasated blood was present among the superficial fibers of

the left ventricle. The lesions in the right ventricle, however, were most marked. Hemorrhages, edema, and collections of round cells and polymorphonuclear neutrophils were scattered through the entire wall. Many of the muscle fibers were necrotic or absent (Fig. 11). Except for moderate hypertrophy of the muscle fibers in the left ventricle and diffuse scarring in the interventricular septum, no other lesions were seen. No bacteria were stained in the epicardium or myocardium.

In three patients with active rheumatic heart disease, pericarditis was determined by friction rubs and roentgenographic studies in all cases. Serial electrocardiograms showed no significant RS-T changes. No deaths occurred.

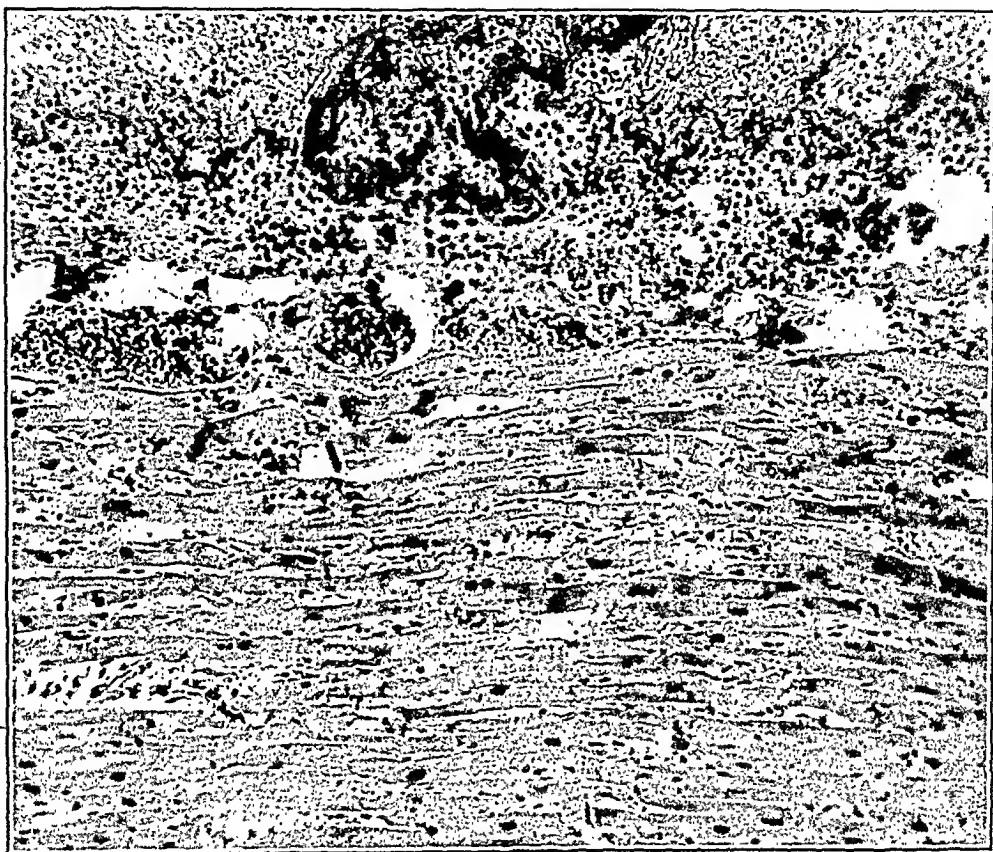


Fig. 13.—A section of the left ventricle from a case of pneumococcal pericarditis which showed no electrocardiographic changes. The fibrinopurulent epicardial exudate does not invade the myocardium and the muscle fibers are not degenerated.

Three patients with uremic pericarditis likewise showed no significant changes in the electrocardiograms. In the two cases examined at autopsy, extensive fibrinous pericarditis was present, accompanied by 60 c.c. and 300 c.c. of serous fluid. The inflammatory epicardial exudate did not invade the myocardium in many sections of both auricles and ventricles. The muscle fibers were hypertrophied but not degenerated (Fig. 12).

Two of the patients with lobar pneumonia and pericarditis had normal electrocardiograms. Marked fibrinopurulent pericarditis in both was associated with 40 c.c. and 350 c.c., respectively, of pericardial



fluid. Microscopically, the purulent exudate in the epicardium did not invade the myocardium in numerous sections from the auricles and ventricles (Fig. 13) except in three small areas in one case. No degenerative changes were seen in the muscle fibers.

#### DISCUSSION

In this study a direct chest lead was used in all but two of the patients. This lead was taken by placing the precordial electrode on the fifth left intercostal space in the midclavicular line and the indifferent electrode on the left leg (Lead V of Wolferth and Wood).

The electrocardiographic changes in five of seven cases of purulent pericarditis and in the case of hemopericardium are similar and seem characteristic enough to be of diagnostic value. The typical finding is elevation of the R-T segments in Leads I, II, and III, usually most marked in Lead II. Slurring of the descending limb of the R-wave frequently occurs. In four of the cases, these changes were primarily in Leads I and II and in two cases were mainly in Leads II and III. A definite Q-wave in Lead III was seen in only one case. In the four cases having typical electrocardiographic changes in which the chest lead was obtained, no significant abnormalities were seen in this lead.

The resemblance of electrocardiograms in pericarditis to those in acute myocardial infarction has been commented on in the literature. An electrocardiogram with no reciprocal action of the RS-T segment in Leads I and III and with the greatest elevation of the R-T segment in Lead II is not typical of either an anterior or posterior infarct. Because Lead II shows a summation effect of the changes in Leads I and III, myocardial infarction involving both the anterior and posterior surfaces of the left ventricle may produce changes of this type (i.e., elevation of the R-T segment in all leads, greatest in Lead II). In this combined infarction, however, a well-developed Q pattern or changes in the chest lead, or both, should be present. The electrocardiographic changes described in our cases, therefore, are not characteristic of any type of myocardial infarction.

Cardiac tamponade is the usual explanation given in the literature for the changes in the RS-T segment. In some patients, however, moribund with tamponade from hemopericardium, normal electrocardiograms have been obtained before operation.<sup>1,7</sup> Of our six patients with "positive" electrocardiograms, three had no appreciable increase in the amount of pericardial fluid. Five patients with no electrocardiographic changes had increased amounts of pericardial fluid by x-ray films or at autopsy. Our first case, moreover, showed a return of the elevated R-T segments to normal while the amount of pericardial fluid was increasing (Fig. 1). In this small series of cases, therefore, we can see no relation between the amount of peri-

cardial fluid and electrocardiographic changes. The progressive electrocardiographic changes in many cases of stab wound of the ventricle<sup>6, 7, 8</sup> suggest acute pericarditis rather than a single anterior lesion of the myocardium. In our case of this type, the lesion was in the auricle and the changes in the ventricular complexes of the electrocardiogram could not have been caused by the stab wound.

In three of the cases with purulent pericarditis, microscopic study showed inflammatory and degenerative changes of the superficial myocardium. Where the epicardial fat was thick the underlying myocardium appeared normal. In Case 1, although groups of superficial muscle fibers appeared to have been replaced by scar tissue, no active inflammation was present in the myocardium. The two blocks from the left ventricle, in Case 4, were covered with thick layers of epicardial fat and the subjacent myocardium showed no lesions. Myocarditis was, however, present in the right auricle even at a distance from the line of suture. In Case 6, with hemopericardium, not enough blocks were available for study, but large areas of hemorrhage, edema, and cellular infiltration were present in the right ventricle. In the two cases of pneumococcic, and the two of uremic pericarditis, in which no electrocardiographic changes occurred, careful study showed no significant inflammatory changes of the myocardium. *It is, therefore, believed that the electrocardiographic changes reported are the result of superficial myocarditis.* Involvement of both the anterior and posterior surfaces of the ventricles would explain the summation effect of the R-T segment in Lead II. The absence of deeper myocardial damage might account for the lack of any well-developed Q-wave patterns or of significant changes in the chest lead.

If myocardial inflammation is present, it is probable that some cases of nonsuppurative pericarditis would show similar electrocardiographic changes. It is also likely that in some cases of purulent pericarditis electrocardiographic changes may be transient.

#### SUMMARY

1. Studies on fourteen cases of acute pericarditis are presented. Seven of these cases were purulent in type and six were serous. One followed hemopericardium.

2. Similar changes in the electrocardiograms were present in five of the seven cases of purulent pericarditis. Less marked changes occurred in the case of hemopericardium. In the remaining cases, such abnormalities were not found.

3. The characteristic electrocardiographic pattern consists of an elevation of the R-T segments in the three limb leads. This change is often most striking in Lead II. Slurring of the descending limb of the R-wave is frequent. A normal chest lead (apex of heart and left

leg), the absence of a reciprocal action of the RS-T segments in Leads I and III, and no well-developed Q pattern, differentiate this condition from acute myocardial infarction.

4. In this series of cases, we find no relation between the amount of pericardial fluid and electrocardiographic changes.

5. Microscopic study of the hearts in all cases with "positive" electrocardiograms showed definite subepicardial myocarditis. Autopsies were obtained in four cases with normal electrocardiograms. In none was the pericarditis associated with inflammation of the myocardium.

#### REFERENCES

1. Schwab, E. H., and Herrmann, G.: Alterations of the Electrocardiogram in Diseases of the Pericardium, *Arch. Int. Med.* 55: 917, 1935.
2. Scott, R. W., Feil, H. S., and Katz, L. N.: The Electrocardiogram in Pericardial Effusion. I. Clinical, *AM. HEART J.* 5: 68, 1929.
3. Harvey, J., and Scott, J. W.: Changes in the Electrocardiogram in the Course of Pericardial Effusion With Paracentesis and Pericardiectomy, *AM. HEART J.* 7: 532, 1932.
4. Purks, W. K.: The Occurrence of a Coronary T-Wave in Purulent Pericarditis, *South. M. J.* 24: 1032, 1931.
5. Master, A. M., Romanoff, A., and Jaffe, H.: Electrocardiographic Changes in Pneumonia, *AM. HEART J.* 6: 696, 1931.
6. Koucky, J. D., and Milles, G.: Stab Wounds of the Heart, *Arch. Int. Med.* 56: 281, 1935.
7. Elkin, D. C., and Phillips, H. S.: Stab Wound of the Heart, Electrocardiographic Studies of Two Cases, *J. Thoracic Surg.* 1: 113, 1931.
8. Porter, W. B., and Bigger, I. A.: Nonfatal Stab Wounds of the Ventricles, *Am. J. M. Sc.* 184: 799, 1932.
9. Barnes, A. R.: Electrocardiographic Pattern Observed Following Acute Coronary Occlusion Complicated by Pericarditis, *AM. HEART J.* 9: 734, 1934.
10. Wolferth, C. C., and Wood, F. C.: Acute Cardiac Infarction Involving Anterior and Posterior Surfaces of the Left Ventricle, *Arch. Int. Med.* 56: 77, 1935.
11. Katz, L. N., Feil, H. S., and Scott, R. W.: The Electrocardiogram in Pericardial Effusion. II. Experimental, *AM. HEART J.* 5: 77, 1929.
12. Herrmann, G., and Schwab, E. H.: Some Experimental and Clinical Electrocardiographic Observations on R-S-T and T Changes in Pericarditis, *Tr. A. Am. Physicians* 49: 229, 1934.
13. Barnes, A. R., and Mann, F. C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
14. Fowler, W. M., Rathe, H. W., and Smith, F. M.: The Electrocardiographic Changes Following the Ligation of the Small Branches of the Coronary Arteries, *AM. HEART J.* 8: 370, 1933.

# THE CIRCULATION TIME OF THE BLOOD OF DOGS, DETERMINED BY IONIZATION (GEIGER COUNTER) METHODS

## I. THE EFFECTS OF PHYSICOPHYSIOLOGICAL AGENTS AND OF DRUGS

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THE circulation time of the blood between two chosen points in the body may be defined as the time between the injection of a substance at one point and the detection or registration of its arrival at the second point by means of its color, vasodilator or vasoconstrictor effects, neuromuscular stimulation, effects on the electrical properties of the blood, fluorescence, or radioactive qualities. In our investigations the time of circulation of the blood of dogs was measured between a point in the jugular vein and a point in that portion of the superficial femoral artery lying in the adductor canal. The ensemble of apparatus which was used is a modification suggested by the researches of Blumgart<sup>1</sup> and his colleagues. Essentially the apparatus consists of: (1) an ionization chamber, often referred to in the literature of physics as the Geiger counter; (2) a source of high voltage (approximately 2,500 V.) for the ionization chamber; (3) three stages of amplification with their own power supplies; and (4) a mechanism for recording the receipt of ionizing energy or changes in ionization in the Geiger chamber. Details concerning the ensemble of apparatus and its *modus operandi* are to be found in a communication published elsewhere.<sup>2</sup>

The radioactive material used as the ionization agent consisted of 1 to 2 c.c. of a solution containing the disintegration products obtained from 3 to 5 millicuries of radon (radium emanation). The most active constituent in this solution from the standpoint of gamma radiation is radium C, which has a half period of about twenty minutes and changes to radium D. In two to three hours the activity of the injected radioactive material decayed sufficiently to permit the use of the same animal in other tests during the day.

The procedure in determining the circulation time of the blood consisted in the proper placement of the ionization chamber over the superficial femoral artery, the injection of the radioactive material into the jugular vein, the automatic recording (on an apparatus carrying a strip

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of paper moving at a uniform and known rate) of the time which elapsed between injection and arrival of active material under the aluminum window of the ionization chamber. Figure 1 is a reproduction, on a reduced scale, of a typical record. Since the speed of the paper on which records were made is known, it is possible to convert the recorded distance between the period of injection and arrival of radioactive material into the time of circulation of the blood between the two points.

This method and procedure are particularly advantageous in investigations of this character because there is: (1) lack of trauma, (2) deletion of reaction periods, (3) the ability to use trained animals, (4) the possibility of using the same animal repeatedly, and (5) immediate and positive detection of the arrival of the injected material.

#### THE CIRCULATION TIME OF THE BLOOD UNDER BASAL CONDITIONS

The circulation time of the blood (using trained dogs) between the jugular vein and the superficial femoral artery lying in the adductor canal was taken to be its basic value when the animal, after a twenty-

Period of injection	Arrival of radioactive material beneath ionization chamber
<b>A</b>	<b>B</b>
DATE - 3 8 34	INJECTION TIME - 2:05 p.m.
DOG No. R2	INJECTION - From right jugular
ANESTHESIA - Ether	to left femoral
PULSE - 158	ROOM TEMP. - 24.5° C.
RESPIRATION - 60	REMARKS - Dog fed in morning

Fig. 1.—Reproduction of an original record (reduced approximately a third). The circulation time of the blood in this case is 6.5 seconds as determined from the time of passage of the radioactive material from the jugular vein (A) to the receipt of the active material in the femoral artery (B).

four-hour fast, was under conditions of complete rest on the table, with a pulse rate which was constant for at least five minutes. Under these conditions there were variations in the circulation time of the blood of each dog. For purposes of comparison in other portions of these investigations, a basic normal circulation time was determined for each dog by averaging a considerable number of values obtained for the time of circulation. Table I is a compilation of values of basic normal circulation time and germane data. These basic circulation times ranged from 6.75 to 15.6 seconds for the various dogs used. The data (recorded in part in Table I) show that there is no apparent relationship between the time of circulation of the blood and age, sex, physical condition, or weight of the animals. In contrast, however, the data show that the number of heartbeats which occurred during a specified time of circulation was very nearly the same in all dogs, irrespective of the wide differences in circulation time. The range of values of heartbeats per circulation time was between 13.0 and 16.38; the average value is 14.5 heart-

beats per circulation time. Further investigations are in progress concerning the possibility of establishing a relationship between pulse rates and circulation times to the end that, under the criteria stated, the time of circulation between the points specified may be empirically determined.

TABLE I  
BASIC NORMAL CIRCULATION TIME

DOG	WEIGHT, KG.	NUMBER OF DETERMINATIONS	RANGE OF NORMAL CIRCULATION TIME (JUGULAR VEIN TO FEMORAL ARTERY), SEC.	BASIC NORMAL CIRCULATION TIME, SEC.	RANGE OF PULSE RATE, PER MIN.	BASIC NORMAL PULSE RATE, PER MIN.	HEARTBEATS PER CIRCULATION TIME
1	16.0	3	12.0 to 15.0	13.53	56 to 64	60.0	13.5
2	7.5	8	9.0 to 13.0	11.25	66 to 80	71.5	13.4
3	17.0	9	12.0 to 16.5	14.05	54 to 72	59.0	13.0
4	17.0	4	6.0 to 8.0	6.75	104 to 120	116.0	13.05
5	16.5	3	9.0 to 12.5	10.83	67 to 87	78.0	14.1
6	17.0	5	14.0 to 17.5	15.6	58 to 70	62.0	16.1
7	15.0	4	9.5 to 12.5	11.1	78 to 90	84.0	15.45
8	12.0	4	9.5 to 13.0	11.5	80 to 90	85.5	16.38
9	14.0	3	7.0 to 10.0	8.0	100 to 106	102.0	13.6
10	12.0	3	7.0 to 10.0	8.5	102 to 117	109.0	15.5

#### EFFECTS OF VARIOUS PHYSICOPHYSIOLOGIC AGENTS ON THE CIRCULATION TIME

*Exercise.*—The results of our experiments show that the time of circulation was decreased very markedly immediately after exercise (one to two hours on a treadmill traveling at 1.7 miles per hour), the decreases ranging from 36 to 48 per cent of the control (normal basic) values. Computed from the standpoint of changes in velocity, the range of decrease was from 56 to 95 per cent. These findings are in close agreement with the range of changes in the pulmonary velocity obtained by Ellis.<sup>3</sup> The increase in pulse rate nearly paralleled the changes in velocity, as is evidenced by the fact that the number of heartbeats per circulation time remained approximately the same (within 10 to 15 per cent) as in the normal basic conditions. The fact that the number of heartbeats per circulation time was reduced in every case would lead to the inference that, during exercise, not only the pulse rate but also the stroke output increased.

*Effects of Low Environmental Temperatures.*—During the winter months several of the dogs used in this series of investigations were removed from an environment of 25° C. and placed for an hour or more outdoors at a temperature below 0° C. A sample set of data is: at a room temperature of 25° C., the pulse rate was 60 per minute and the circulation time of the blood 14.1 seconds; after being outdoors and subsequently removed to a room temperature of 17° C., the pulse rate was

79 and the circulation time 12.0 seconds; normal basic heartbeats per circulation time were 14; after being in the cold environment, 15.8. Our data show that the number of heartbeats per circulation time was increased subsequent to being in the cold environment, the average percentage increase (12.6 per cent) being slightly higher in value than the average percentage decrease (10.4 per cent) after exercise.

*Effects of High Environmental Temperatures.*—Each of the dogs was subjected to measurement under environmental temperatures of 29, 37.5, and 41° C. ( $\pm 1^\circ$  C.), respectively. In each instance the animal remained on the observation table in the room at the specified temperature for nearly two hours prior to the determination of the circulation time. We found that there was no significant change in the circulation time of the blood unless the body temperature of the animal rose above normal values (approximately 39° C.). Under these conditions, with a rise of body temperature of about 1° C., the pulse rate increased markedly and there was a very decided decrease in the circulation time. When placed in an environmental temperature of 40° C., the increases in the pulse rates of two dogs were 22 and 55 per cent respectively, whereas the decreases in circulation time were 32 and 47 per cent. The number of heartbeats per circulation time remained practically constant, ranging from 15.5 to 16 in one dog and from 16.4 to 16.8 in the second dog.

#### DRUGS WHICH DECREASE THE CIRCULATION TIME

The general procedure for testing the effects of various drugs on the circulation time was the same in all cases. The normal basic circulation time was determined, followed by an interval of two to three hours to allow the disintegration products of the injected radioactive material to decay to values which did not produce responses in the Geiger chamber. The drug was then injected and, after a predetermined period of time (which varied for the different drugs used), another portion of the radioactive solution was introduced through the same needle, and the time of circulation of the blood determined. The administration of thyroxin, histamine, and ether anesthesia decreased the circulation time in the order named; increases in circulation time were produced by eobefrin, epinephrine, nicotine, pitressin, and pituitrin, respectively, in the sequence stated.

*Thyroxin.*—The basic circulation time of the blood of each of the dogs used was determined. Each animal was then given 1 c.c. of a (1 mg. per c.c.) solution of thyroxin per kilogram of body weight on two successive days. The circulation time was determined on the third day. Marked reductions in the values of the circulation time were found; the percentage decreases ranged from 21 to 51 per cent. Such decreases in circulation time are in conformity with the increases of minute volume blood flow in the femoral artery of a dog after feeding of desiccated

thyroid gland as found by Herrick, Essex, Mann, and Baldes.<sup>4</sup> A fairly uniform decrease in the number of heartbeats per circulation time was evident in all cases, the decrease ranging from 16 to 25 per cent.

*Histamine.*—The radioactive solution was injected one minute after the injection of 1 mg. of histamine. In all cases there was a marked increase (ranging from 60 to 95 per cent) in the pulse rate and a corresponding decrease (ranging from 110 to 40 per cent) in the time of circulation of the blood subsequent to the injection of the drug. The number of heartbeats per circulation time was increased (about 10 per cent) in two dogs and decreased in two other animals.

*Ether.*—Ether anesthesia was maintained by the auto-inhalation method; the depth of anesthesia was that which is commonly spoken of as "surgical" ether anesthesia. Sheard, Rynearson, and Craig,<sup>5</sup> by measurements of the temperature changes of the extremities, and Herrick, Essex, and Baldes,<sup>6</sup> by direct determinations of changes in blood flow, demonstrated that surgical ether anesthesia is nearly, if not equally, as effective in producing vasodilatation of the blood vessels of the dog as sympathectomy. It was of interest, therefore, to determine the change in circulation time produced by this agent. In every case (4 dogs) the circulation time was decreased, the percentages of decrease ranging from 21.5 to 54.5. The pulse rates increased within the range of 120 per cent to nearly 200 per cent. The number of heartbeats per circulation time was increased within a range of 13.5 to 57 per cent.

#### DRUGS WHICH INCREASE THE CIRCULATION TIME

*Epinephrine (cobefrin).*—In every case 1 c.c. of 1:1000 solution of epinephrine or the equivalent strength of cobefrin per kilogram of body weight was administered prior to the injection of the radioactive material, the same needle being used for the two injections. A series of controlled experiments, injecting equivalent dosages of epinephrine or cobefrin (concentration fivefold as great as epinephrine) into the same animal, were carried out under similar conditions of time of injection of drug previous to the introduction of the ionizing agent. No differences in the effects of the two drugs or the time of circulation of the blood could be detected.

The circulation time of the blood and the number of heartbeats per circulation time are markedly affected by the period of time intervening between the injections of the epinephrine and of the ionizing agent used for the determination of the circulation time. The results obtained in the case of a dog having a basic normal circulation time of 8.5 seconds and basic normal pulse rate of 109 per minute subsequent to intervals of 30, 60, 90, 120, 180, and 240 seconds between intravenous injection of epinephrine (0.11 c.c. in each instance) and the determination of the circulation time, are shown in Fig. 2. Data of a similar character were



obtained from experiments on other dogs. The maximal increase in circulation time (from 8.5 to 26 seconds, Fig. 2) was obtained sixty seconds after the injection of epinephrine. The time of circulation of the blood returned to its basic value about 120 seconds after injection of the drug, no appreciable changes in the circulation time occurring at intervals of 180 and 240 seconds after the injection. In brief, the circulation time of the blood is increased over 200 per cent, the pulse rates are decreased about 10 per cent (for example, from 109 to 96 per minute) and the number of heartbeats per circulation time is increased 200 per cent at 60 seconds after injection. The curve (dotted line, Fig. 2) correlating the number of heartbeats per circulation time and the

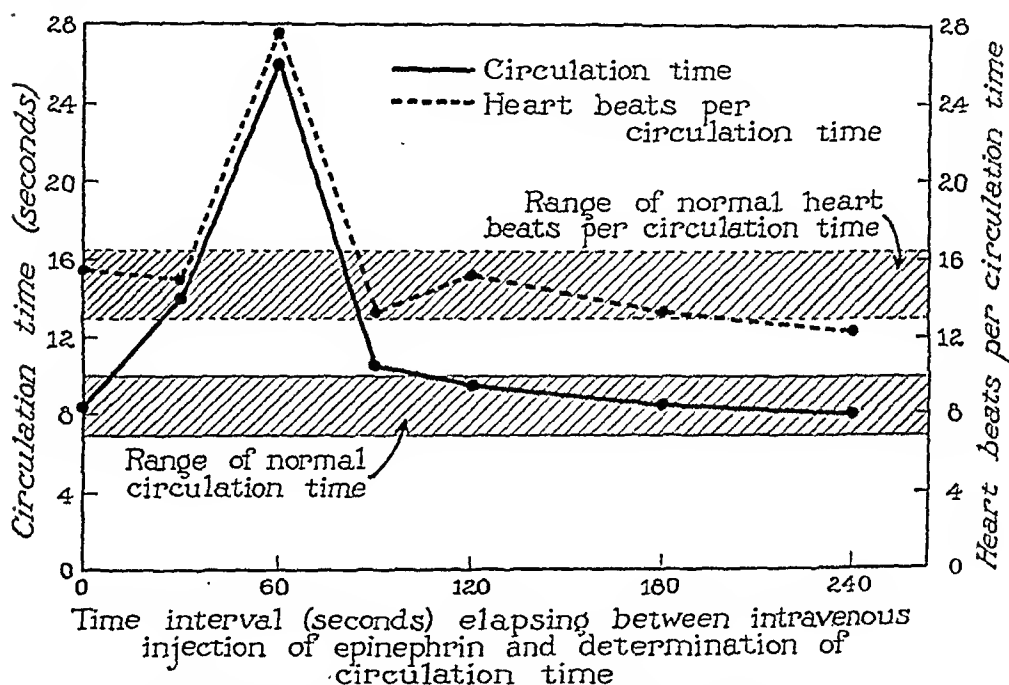


Fig. 2.—Curves showing the relationships between the circulation time of the blood in seconds, the number of heartbeats per circulation time and the periods of time after the injection of epinephrine.

period of time elapsing after the injection of epinephrine practically parallels the course of the curve of circulation time.

Various controversies have arisen concerning the action of epinephrine; some investigators have reported increased circulation times while other workers have obtained decreases. In none of our observations have we found any indication of a speeding-up of the circulation between the jugular vein and right femoral artery after the intravenous administration of epinephrine in dogs.

*Nicotine.*—In two dogs, in which the time elapsing between the injection of the nicotine and the radioactive material was short, namely, 15 and 8 seconds, there was an increase of the circulation time of 48 (from 11.5 seconds to 17 seconds) and 78 (from 9 seconds to 16 seconds)

per cent, respectively. In two dogs higher pulse rates were recorded (73 and 78 per cent), whereas in the other two animals decreased pulse rates (31 and 26 per cent) were noted. In all instances the number of heartbeats per circulation time was increased, the increase ranging from 23 (for example, 7.8 to 9.5 heartbeats) per cent to 314 (for example, 14 to 58 heartbeats) per cent.

*Pituitrin and pitressin.*—Intravenous injections of these drugs, in dosages (0.2 to 0.5 mg.) somewhat higher than those therapeutically administered to man, were made 60 or 90 seconds prior to the injection of the radioactive material. A very large increase in the circulation time was observed in all animals. On account of the marked vasoconstrictor action of these drugs, it was difficult to determine accurately the time of arrival of the radioactive material. The increases in circulation time ranged from 125 to 400 per cent after the injection of pituitrin, and from 285 to 510 per cent after the injection of pitressin. The difference between the ranges for the two drugs is not to be considered as significant because of the difficulty of obtaining and interpreting the records. The number of heartbeats per circulation time was increased; the ranges of increase were 135 to 170 per cent for pituitrin and 100 to 175 per cent for pitressin. Geiling, Herrick, and Essex<sup>7</sup> have shown that there is a marked decrease in the minute volume blood flow in the femoral and carotid arteries of the dog after injections of either pituitrin or pitressin.

#### COMPILATION OF DATA ON THE SAME DOG

We were fortunate enough to be able to carry two or three dogs through the whole series of experiments. Table II contains the data

TABLE II

COMPILATION OF DATA CONCERNING CIRCULATION TIME OF THE BLOOD AND NUMBER OF HEARTBEATS PER CIRCULATION TIME AFTER THE USE OF VARIOUS PHYSICOPHYSIOLOGIC AGENTS AND DRUGS IN THE SAME DOG

DECREASE OF CIRCULATION TIME			INCREASE OF CIRCULATION TIME		
AGENT OR DRUG	CIRCULATION TIME, SEC.	HEART- BEATS PER CIRCULATION TIME	DRUG	CIRCULATION TIME, SEC.	HEART- BEATS PER CIRCULATION TIME
Normal	16.5	15.5	Normal	16.5	15.5
Chilling	12.0	15.8	Cobefrin	23.0	23.0
Exercise	10.5	12.0	Epinephrine	26.0	21.7
Thyroxin	11.0	12.4	Nicotine	38.5	29.5
Histamine	8.5	17.4	Pitressin	76.0	38.0
Ether	8.0	22.0	Pituitrin	86.0	37.3

concerning the normal basic circulation time of the blood and number of heartbeats per circulation time before and after the administration of the various physicophysiologic agents and drugs cited.

## CONCLUSIONS

Using well-trained dogs, lying at rest on the table for about an hour prior to test and subsequent to a twenty-four-hour fast, we believe that our findings show that:

1. Injection of the rapid disintegration products of radon (radium emanation) at one point in the circulatory system and the detection of their arrival at another point in this system by means of an ionization chamber (Geiger counter apparatus) and amplifying system is a very accurate method for determining the circulation time of the blood.

2. There is a wide variation in the circulation time of the blood between the jugular vein and femoral artery in the various dogs, in the basal state, used in these investigations. There are also considerable variations in the individual basal circulation times.

3. There is no relationship between the circulation time of the blood and age, sex, physical condition, or weight of dog.

4. The number of heart beats per circulation time between the jugular vein and femoral artery tends to be the same in all dogs.

5. Exercise and placing in low environmental temperatures decrease the circulation time of the blood as well as slightly decreasing the number of heartbeats per circulation time.

6. Increase of environmental temperature does not alter the circulation time until the rectal temperature rises above its normal value. When this temperature is exceeded, the circulation time is markedly decreased with little, if any, change in the number of heartbeats per circulation time.

7. The administration of thyroxin (1 mg. per kilogram of body weight per day for two days prior to test) produces a decrease in circulation time.

8. Histamine and ether anesthesia produce a marked decrease in circulation time.

9. Nicotine, pituitrin, and pitressin cause marked increases in the circulation time and a large increase in the number of heartbeats per circulation time.

10. Epinephrine and cobefrin in equivalent dosage produce the same effect on the circulation time and the number of heartbeats per circulation time.

11. After the injection of epinephrine, the circulation time of the blood increases to a maximal value at sixty seconds, returns to normal values after two minutes and remains in the normal range thereafter.

## REFERENCES

1. Blumgart, H. L., and Yens, O. C.: Studies on the Velocity of Blood Flow. I. The Method Utilized, *J. Clin. Investigation* 4: 1, 1927.
2. McCracken, E. C., Sheard, Charles, and Essex, H. E.: An Ensemble for the Determination of the Circulation Time of the Blood by an Ionization (Geiger Chamber) Method, *Proc. Soc. Exper. Biol. & Med.* 36: 106, 1937.

3. Ellis, L. B.: Circulatory Adjustments to Moderate Exercise in Normal Individuals With Particular Reference to the Inter-Relation Between the Velocity and Volume of the Blood Flow, *Am. J. Physiol.* 101: 494, 1932.
4. Herrick, J. F., Essex, H. E., Mann, F. C., and Baldes, E. J.: The Effect of Feeding Desiccated Thyroid Gland on the Flow of Blood in the Femoral Artery of the Dog, *Am. J. Physiol.* 105: 434, 1933.
5. Sheard, Charles, Rynearson, E. H., and Craig, W. McK.: Effects of Environmental Temperature, Anesthesia, and Lumbar Sympathetic Ganglionectomy on the Temperatures of the Extremities of Animals, *J. Clin. Investigation* 11: 183, 1932.
6. Herrick, J. F., Essex, H. E., and Baldes, E. J.: The Effect of Lumbar Sympathectomy on the Flow of Blood in the Femoral Artery of the Dog, *Am. J. Physiol.* 101: 213, 1932.
7. Geiling, E. M. K., Herrick, J. F., and Essex, H. E.: The Effect of Posterior Pituitary Preparations on the Blood Flow of the Normal Intact Dog, *J. Pharmacol. & Exper. Therap.* 51: 18, 1934.

# THE CIRCULATION TIME OF THE BLOOD OF DOGS, DETERMINED BY IONIZATION (GEIGER COUNTER) METHODS

## II. THE EFFECTS OF DIGESTION

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THE ensemble of apparatus used and methods followed for obtaining the circulation time of the blood are described in another communication.<sup>1</sup> In brief, the procedure consists in the injection of a solution containing small quantities of the disintegration products of radon (radium emanation) into the jugular vein and obtaining the time of passage of the radioactive substance between the jugular vein and the femoral artery lying in the adductor canal, by the use of an ionization (Geiger counter) chamber.

The circulation time (in seconds) of the blood between the two specified points and the pulse rate per minute were determined after the animal had been fasted for twenty-four to one hundred ninety-two hours. Observations previously made during investigations on the circulation time of the blood demonstrated that the injected radioactive material did not decay to values sufficiently low to permit the use of the dog for further tests until two or three hours had elapsed, hence the number of determinations of the circulation time is limited to three in each working day. Subsequent to the determination of the basic circulation time following the period of fasting, the dog was allowed to remain at rest for about two and one-half hours, after which it was returned to the observation table and fed a meal consisting of 1 gm. of glucose for each kilogram of body weight, and from two to four eggs in 400 to 600 c.c. of milk (depending on the weight of the animal); or, in certain cases, a meal was made of meat and cereal. After completion of feeding, pulse rates were taken and closely followed until the rate had increased considerably above that which was obtained before the ingestion of food. When it was found that the increased pulse rate was maintained quite constant for a period of ten or more minutes, a second determination of the circulation time was made.

Data concerning the circulation time of the blood before and during the digestion of food, pulse rates, and types of meal ingested are

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TABLE I  
EFFECTS OF DIGESTION ON THE CIRCULATION TIME OF THE BLOOD

DOG	WEIGHT, KG.	LENGTH OF FASTING, HR.	CIRCULA- TION TIME BEFORE FEEDING, SEC.	PULSE RATE BE- FORE FEED- ING, PER MIN.	TYPE OF MEAL*	TIME OF FEEDING TO INJEC- TION, MIN.	CIRCULA- TION TIME AFTER FEEDING, SEC.	PULSE RATE AFTER FEEDING, PER MIN.	HEART- BEATS PER CIRCULA- TION TIME BEFORE FEEDING	HEART- BEATS PER CIRCULA- TION TIME AFTER FEEDING	INCREASE IN PULSE RATE AFTER FEEDING, %	DECREASE IN CIRCU- LATION TIME AFTER FEEDING, %
1	7.5	24	9.0	80	1	70	6.5	91	12.0	9.85	13.7	27.8
		48	17.0	52	1	80	12.0	86	14.7	17.2	65.5	29.4
		120	13.5	56	2	220†	10.5	76	14.8	13.3	15.1	22.2
2	17.0	24	14.5	56	1	30	12.5	64	13.5	13.3	14.0	12.9
		24	13.5	60	2	50	11.0	70	13.5	12.8	16.6	18.5
		48	15.0	52	1	35	11.5	72	13.5	12.8	36.5	18.5
		48	16.5	48	2	62	13.5	60	13.2	13.5	25.0	18.2
		120	14.5	57	1	43	12.5	68	13.5	14.2	19.3	12.9
3	16.0	48	16.0	56	1	28	11.0	96	14.9	17.6	71.5	31.2
		48	17.1	50	2	48	12.1	84	14.15	16.8	68.0	29.4
4	17.0	48	7.0	104	1	32	5.5	110	12.1	10.1	5.7	21.4
		96	10.0	86	1	48	7.5	114	14.3	14.3	32.6	25.0
5	16.5	48	12.0	64	1	108†	8.0	96	12.8	12.8	50.0	33.3
		192	11.0	74	1	60	7.5	100	13.6	12.5	35.0	31.8
6	17.7	72	18.0	60	1	64	11.5	68	18.0	13.0	13.3	36.1
7	20.0	48	20.0	86	1	99†	14.5	125	28.6	30.2	45.3	27.5
8	14.0	24	15.0	106	1	115†	12.0	128	26.5	27.7	20.0	20.0
9	17.0	48	27.5†	42	1	45	15.1	80	19.25	20.0	90.5	45.4

\*Type of meal: (1) milk, egg, glucose; (2) meat and cereal.

†Injection made at the time of maximal volume flow of blood per minute.

‡Left saphenous vein to right femoral artery.

given in Table I. In toto, these investigations demonstrate that the circulation time of the blood in dogs which have been fasted for twenty-four or more hours is decreased 12.9 to 45.4 per cent during the course of digestion (presumably at its maximal point as judged by the highest rate of pulse). At first glance it might appear that there is a greater decrease in the circulation time after a forty-eight-hour fast than after a twenty-four-hour fast. An average of the data for the eight dogs used indicates an additional reduction of about 7 per cent in the circulation time after a forty-eight-hour fast. In the same dog, however, the circulation time is practically the same subsequent to the two periods of fasting. On the other hand, the percentage decrease in circulation time appears to be significantly less after a one-hundred-twenty-hour fast as compared to the results after a fast of twenty-four or forty-eight hours.

A comparison of pulse rates with time of circulation shows that, after a twenty-four-hour fast, the percentage decrease in circulation time was approximately the same as the percentage increase in pulse rate. In eight of the nine dogs subjected to a forty-eight-hour fast the percentage decreases in circulation time were very much less than the percentage increases in pulse rate. No apparent relationship exists between the two when longer periods of fast were given.

An inspection of the data relative to the number of heartbeats per circulation time shows that there were increases (average per cent increase, 9.2) in eight instances, decreases (average per cent decrease, 11.5) in eight, and no changes in two instances. There is evidence of a definite tendency for the number of heartbeats per circulation time in an individual dog to remain constant and of approximately the same value before and throughout the cycle of digestion, as well as under the influence of such physico-physiologic agents as exercise and changes in environmental temperature. In contrast, the number of heartbeats per circulation time is markedly affected by various drugs and by ether anesthesia.<sup>2</sup>

#### SIMULTANEOUS MEASUREMENTS ON MINUTE VOLUME FLOW AND CIRCULATION TIME OF BLOOD

Using the Herrick and Baldes<sup>3</sup> modification of the Rein<sup>4</sup> thermostromuhr, we were able to conduct a short series of experiments in which simultaneous measurements of the circulation time (seconds) and rate of volume flow of blood (c.c. per minute) were obtained. In these experiments, the diathermy-thermo-element was placed on the right femoral artery in the adductor canal; the time of receipt of the radioactive material in the left femoral artery, subsequent to injection in the jugular vein, was recorded. By reason of the fact that the radioactive deposits introduced into the body have not sufficiently decayed to permit frequent determinations of circulation time, simultaneous measurements

by the two methods were limited to (1) normal fasting conditions, (2) the height of digestion, and (3) three or four hours after the second set of simultaneous measurements of blood volume flow and circulation time. The height of digestion was based on the determination of the maximal rate of volume flow through the femoral artery as measured by the thermostromuhr method.

Figure 1 gives graphically the relations existing between the rate for one of the dogs in which data were obtained simultaneously by the two experimental methods. Subsequent to a forty-eight-hour fast, the circulation time was found to be 20 seconds (Fig. 1, point *a*, curve 1), the volume blood flow 140 c.e. per minute (curve 2) and the pulse rate 86 per minute (curve 3). The circulation time decreased to 14.5 (point

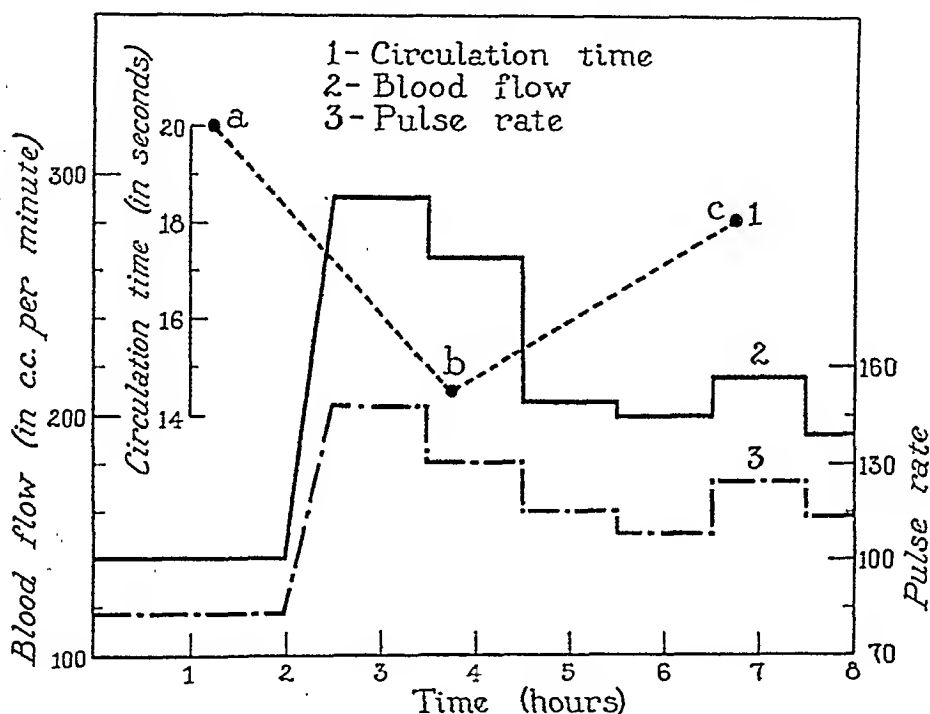


Fig. 1.—Relations between the circulation time of the blood, minute volume blood flow and pulse rate before, and subsequent to, the ingestion of food.

*b*, curve 1) after the ingestion of a milk-egg-glucose meal and at the time the minute volume blood flow was at, or near, its maximal value of 280 c.e. per minute, with a maximal pulse rate of 150 per minute. Three hours later the circulation time of the blood increased to 17.6 seconds (point *c*, curve 1), the pulse rate dropped to 128 per minute and the volume rate of flow decreased to 160 c.e. per minute. These curves and other sets of data (Table II) demonstrate that increases in the volume flow of blood were coincident with decreases in circulation time.

Our investigations corroborate the findings of Herrick, Essex, Mann, and Baldes<sup>5</sup> to the effect that the type of food ingested influences the time of onset and the duration of increased blood flow and pulse rate. Under similar conditions and using the same dog, the maximal increases



TABLE II

CIRCULATION TIME OF THE BLOOD (FROM JUGULAR VEIN TO FEMORAL ARTERY),  
VOLUME BLOOD FLOW (C.C. PER MINUTE), AND PULSE RATES PER MINUTE  
DURING THE DIGESTIVE CYCLE. MILK-EGG-GLUCOSE MEAL.

DOG	WEIGHT, KG.	CIRCULATION TIME, SEC.	BLOOD FLOW, C.C. PER MIN.	PULSE RATE, PER MIN.	TIME INTERVAL FEEDING TO INJECTION, MIN.	CIRCULATION TIME, SEC.	BLOOD FLOW, C.C. PER MIN.	PULSE RATE, PER MIN.	TIME INTERVAL, MIN. AFTER FEEDING	CIRCULATION TIME, SEC.	BLOOD FLOW, C.C. PER MIN.	PULSE RATE, PER MIN.
1	16.5	12.0	184	64	108	8.0	123	96	257	10	90	90
2	17.7	18.2	92	60	65	11.5	292	70	---	--	--	--
3	20.0	20.0	123	86	100	14.5	269	125	373	18	190	114

in pulse rate and volume flow and minimal values of circulation time were found to occur more rapidly after the feeding of a milk-egg-glucose meal than after the ingestion of meat and cereal.

Herriek, Essex, Mann, and Baldes have shown that, during digestion, there is the same type of increase of volume flow in the femoral and carotid arteries and in the external jugular veins as there is in the mesenteric arteries. The results of their experiments also led them to conclude that the increased volume flow of blood during digestion is accounted for chiefly by an increase in the velocity of the blood in the entire circulatory system. Our data support the assumption that an increase in the velocity of flow of blood, evidenced by the decrease in the circulation time of the blood between the jugular vein and the femoral artery, is one of the chief factors.

#### CONCLUSIONS

1. The circulation time of the blood is decreased (12.9 to 45.4 per cent) during digestion, presumably at its maximal point as judged by the highest pulse rate. The type of meal ingested influences the time at which digestion reaches its maximum and at which the circulation time of the blood is at its minimal value.

2. The decrease in the circulation time of the blood during the processes of digestion is coincident with an increase in pulse rate and also with an increase in the volume rate of blood flow per minute in the femoral artery as measured by a modification of the Rein thermomuhur.

3. These findings support the deductions of other investigators concerning the effects of digestion on volume rate of blood flow, since our experiments have demonstrated that an increase in velocity of the blood in the entire circulatory system is the chief factor which accounts for increased rate of blood flow.

## REFERENCES

1. McCracken, E. C., Sheard, Charles, and Essex, H. E.: An Ensemble for the Determination of the Circulation Time of the Blood by an Ionization (Geiger Chamber) Method, *Proc. Soc. Exper. Biol. & Med.* 36: 106, 1937.
2. McCracken, E. C., Essex, H. E., and Sheard, Charles: The Circulation Time of the Blood of Dogs, Determined by Ionization (Geiger counter) Methods. I. The Effects of Physicophysiologic Agents and of Drugs, *AM. HEART J.* 14: 51, 1937.
3. Herrick, J. F., and Baldes, E. J.: The Thermoströmuhr Method of Measuring Blood Flow, *Physics* 1: 407, 1931.
4. Rein, H.: Die Thermo-Stromuhr. Ein Verfahren zur fortlaufenden Messung der mittleren absoluten Durchflussmengen in uneröffneten Gefäßen in situ, *Ztschr. f. Biol.* 87: 394, 1928.
5. Herrick, J. F., Essex, H. E., Mann, F. C., and Baldes, E. J.: The Effect of Digestion on the Blood Flow in Certain Blood Vessels of the Dog, *Am. Jour. Physiol.* 108: 621, 1934.

# ELECTROCARDIOGRAPHY IN INFANTS AND SMALL CHILDREN

## SUGGESTIONS ON THE TECHNIC\*

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THE difficulties of obtaining satisfactory electrocardiographic tracings from infants and small children are well known to those who have attempted this procedure. Several months ago when we began a series of normal control electrocardiograms on newborn infants it became apparent that the percentage of good tracings obtained with adult-sized electrodes was too small to warrant continuing unless the technic could be improved.

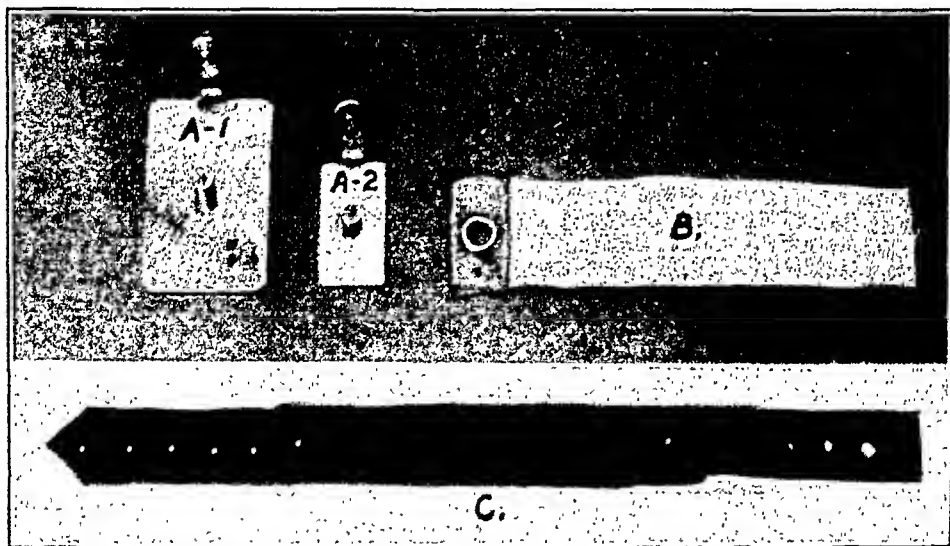


Fig. 1.—A-1, electrode for adults; A-2, electrode for infants; B, retaining strap for extremities; C, retaining strap for chest (approximately  $\frac{1}{8}$  actual size).

The main drawbacks to the use of adults' electrodes were their large size, often resulting in poor electrical contacts when applied to the tiny extremity of an infant, and their weight which resulted in physical restraint and struggling on the part of the infant to free himself. This, in turn, produced the artefacts due to motion so common in infant electrocardiograms.

With these points in mind we have devised a method of obtaining good tracings which, along with the judicious use of a bottle of water and a little patience, has proved satisfactory in every case.

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# APPARATUS

The infant-sized electrodes\* (Fig. 1, *A-2*) used by us were made of German silver, and are of the same general design as the large electrodes now in common use, but measure only 2 by 4 cm. in area as compared with 3.8 by 6.6 cm. which is the area of the adult-sized electrode (Fig. 1, *A-1*). The central post for attaching the small electrode measures 1.25 cm. in height as compared with 1.65 cm. in the adult's electrode.

A strip of elastic webbing 3.5 cm. wide and 15 cm. long, the end of which was reinforced with leather and a small metal ring, was used to apply the electrodes to each extremity (see Fig. 1, *B*).

From a piece of flat rubber 2 mm. in thickness, a strap (Fig. 1, *C*) 2.5 cm. wide and 50 cm. long was made for applying the chest electrode. On one end of this strap large holes (3.5 mm. in diameter) were made to fit over the base of the central electrode-post and on the other end small holes (1.5 mm. in diameter) to fit over the tip of the electrode post.

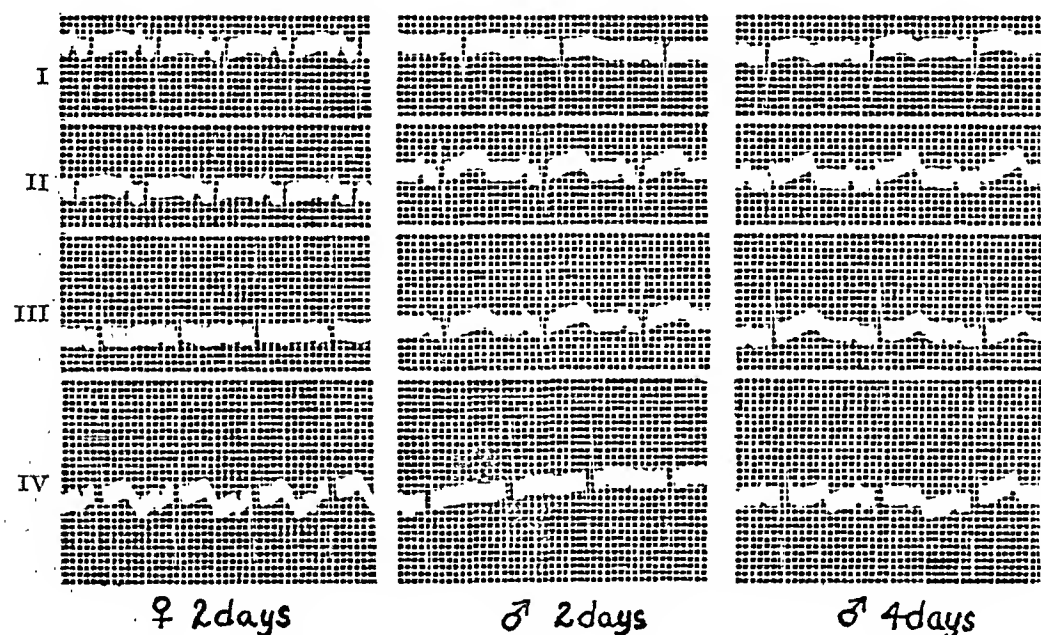


Fig. 2.—Electrocardiograms (Leads I, II, III, and IV) of normal newborn infants.

# METHOD

Sanborn redux paste<sup>1</sup> was used as the contact material in applying the electrodes which were placed on the dorsum of the forearms, on the anterior fleshy portion of the left lower leg, and at the cardiac apex to record the chest lead, the leg electrode being left in place as the indifferent electrode. The sites of application, after being cleansed with alcohol, were rubbed gently with a small amount of redux paste and a daub of paste the size of a small pea was smeared on each electrode before it was put in place. The electrodes on the extremities hold firmly in place when the metal ring on one end of the retaining strap is placed over the central post of the electrode at its base and the loose end carried around the extremity and adjusted to the proper snugness by sinking the sharp point of the post into the elastic webbing. Similarly, in applying the electrode to the chest, one of the larger openings at one end of the rubber strap is placed over the base of the central post of the electrode; the strap is then carried around the chest and the electrode made fast by placing one of the many small holes over the tip of the post.

\*Made by the Sanborn Company, Cambridge, Mass., under the direction of Mr. J. L. Jenks, Jr.

## COMMENT

These modifications in technique are reported because we feel that the good results obtained justify their wider use, and because the cost of the additional necessary equipment is very low. In a report on the "Electrocardiogram in Newborn Infants," which is soon to be published, we will elaborate further on some of the refinements of the technique. Sample tracings are shown in Fig. 2.

## REFERENCE

1. Jenks, J. L., Jr., and Graybiel, Ashton: A New and Simple Method of Avoiding High Resistance and Overshooting in Taking Standardized Electrocardiograms, AM. HEART J. 10: 693, 1935.

## CHARACTERISTIC SERIAL CHANGES IN THE FOURTH LEAD AFTER ACUTE CORONARY THROMBOSIS\*

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THE electrocardiographic changes in the conventional leads following acute coronary occlusion have been studied in detail since the original descriptions by Smith,<sup>1</sup> Herrick,<sup>2</sup> Pardee,<sup>3</sup> and others. It has been stressed that these findings, such as elevated RS-T segment, deeply inverted coved T-waves, or abnormally deep Q-waves, are not constant—that they may change from day to day during the early period (first few weeks or months) of an acute coronary thrombosis.<sup>4, 5</sup> These serial electrocardiographic changes indicate a recent injury to the heart and help distinguish it from an old thrombosis.

With Wolferth and Wood's clinical introduction of chest leads to the study of coronary thrombosis<sup>6a, 6b</sup> (after the experimental work of Wilson<sup>7</sup>), the accuracy of the electrocardiographic diagnosis of coronary occlusion was still further increased. These workers and many others<sup>8, 9, 10, 11, 12, 13</sup> found Lead IV definitely helpful in indicating the presence of acute thrombosis in a certain number of cases in which the conventional leads were normal, or not characteristic of this condition.

As in the conventional leads, the significant findings in the chest lead following acute thrombosis undergo serial changes from day to day. Tracings showing these progressive changes have been published in several reports,<sup>11, 13, 14, 15</sup> but the subject deserves more detailed and specific study. Familiarity with the whole sequence of typical changes occurring serially in Lead IV after acute coronary thrombosis enables one to detect this condition more readily in any single four-lead electrocardiogram examined. It also helps to time the occurrence of the thrombosis, and distinguish an anginal attack from a true thrombosis. These aspects will be discussed later.

The present study was made on twelve consecutive patients, eleven males and one female, diagnosed acute coronary thrombosis in the medical wards of Beth Israel Hospital. (There were three more cases which were not used because death supervened before serial tracings could be taken.) None of the patients had received digitalis for weeks prior to admission; no digitalis was administered during their hospital stay. The electrocardiograms were taken at the bedside several times during the first week, then once or twice a week for the next four to five weeks, the period of observation averaging six weeks. A follow-up

\*From the Medical Service of the Beth Israel Hospital.

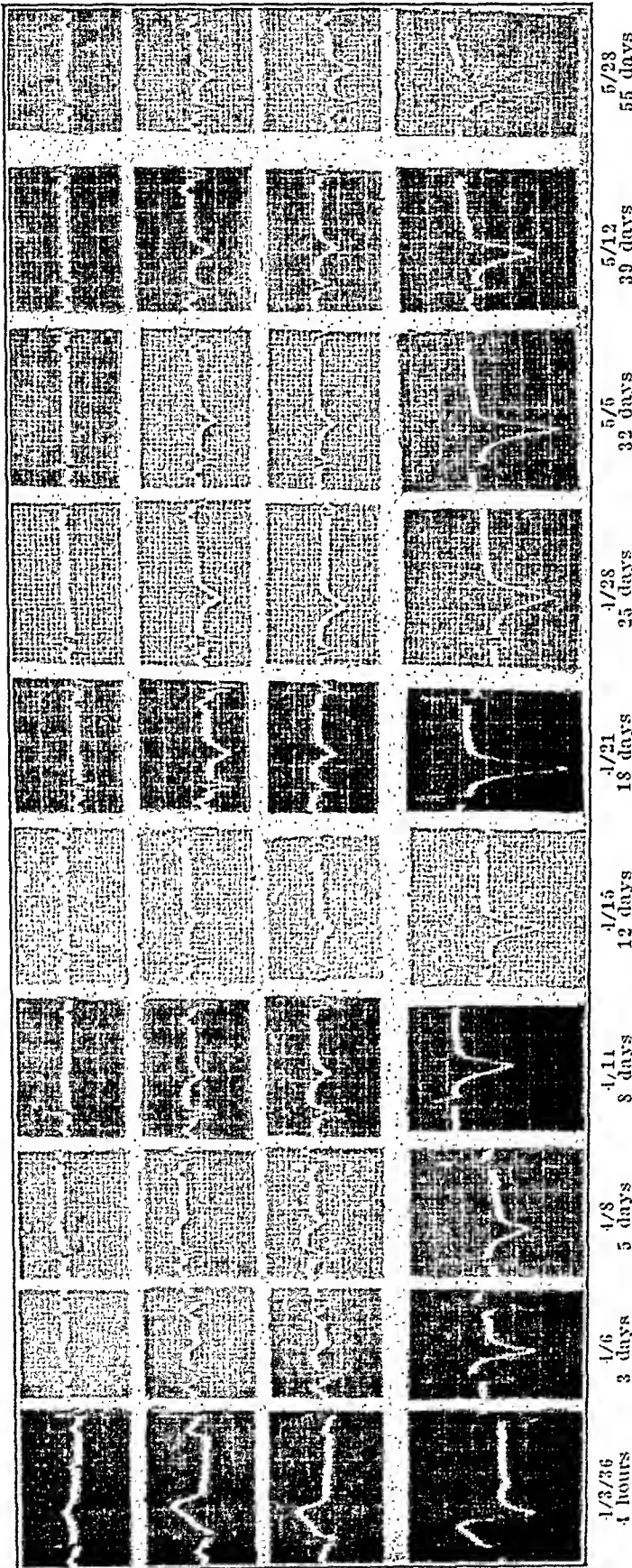


Fig. 1.—Posterior infarction. M. M., No. 31826, male, aged forty-five years. The patient had several attacks of anginal pain for three weeks prior to admission. An anginal attack of unusual severity, not relieved by ultrglycerine or morphine, one hour before admission brought him into the hospital. The first electrocardiogram (April 3, 1936) taken four hours after the attack shows a markedly elevated RS-T segment in Lead IV. The T-wave is negative and already sharply pointed. Note the general similarity in contour of Leads IV, III, and II, and the dissimilarity to Lead I. The fourth lead goes through a period when it appears almost normal (April 8, 1936) except for the raised RS-T segment—a finding much more significant than a similar depression in this lead. The T-wave later (April 11, April 15) becomes suspiciously asymmetrical (cove-planed) in shape; it is already disproportionately large in relationship to the relatively small QRS. The deeply inverted T-waves of April 21 and May 5 are very suggestive of an acute process in the myocardium. In the conventional leads the changes are typical of the Q<sub>2</sub>T<sub>3</sub> type (posterior infarction).

The patient was discharged on May 17, 1936, and readmitted May 27, 1936, because of recurrence of precordial pain and dyspnea. Physical examination revealed no new abnormal findings. The electrocardiogram taken the next day (May 28) shows only the slight serial change pre-dictable from the previous infarction. This lack of electrocardiographic evidence of a new coronary closure in the conventional and the fourth leads helped the clinicians decide that the most recent attack of precordial pain was probably anginal in nature and not due to a new infarction.

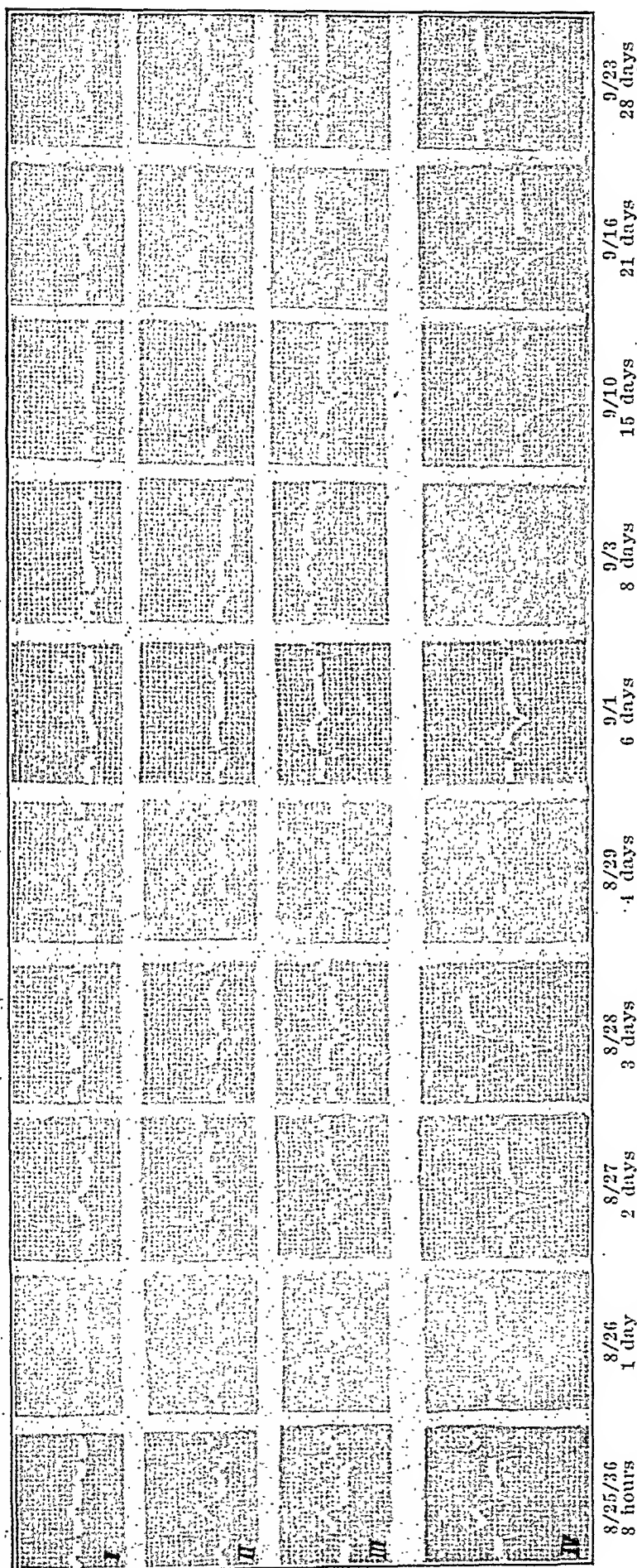


Fig. 2.—Posterior Infarction. W. T., No. 85986, male, aged fifty-six years. The initial electrocardiogram (August 25) taken eight hours after the patient's first attack of substernal pain and oppression shows a markedly elevated RS-T segment in Leads II, III, and IV with normal appearing Lead I. On the next day the RS-T elevation is already much less marked, and the T-wave is becoming inverted. This applies to Leads II and III as well as to Lead IV. In the conventional leads a typical QaT picture is developing. T<sub>a</sub> is now becoming more and more inverted and abnormally deep in relationship to the small, slurred QRS. This deeply inverted T<sub>a</sub> in the presence of a small QRS is extremely suspicious of posterior infarction, especially when the T-wave is asymmetrical and cove-planed, as in this case. There is not much change in Lead IV after Sept. 16, 1936, and it is likely that the small, slurred QRS and relatively deep T will persist for a while. Note the marked similarity in appearance throughout of Leads II, III, and IV in this case of posterior infarction.



electrocardiogram several months later was obtained in four cases. In the chest lead the anterior electrode (a German silver wire closely wound as a watch spring, 15 mm. in diameter) in every instance was placed in the fourth interspace 6 cm. to the left of the midline, and led to the RA terminal of the string galvanometer. The indifferent electrode was attached to the left leg and the LL terminal. The chest electrocardiogram was taken as Lead II, the resistances being kept below 2,500 ohms by light rubbing of the skin with a toothbrush and salt paste.

When the serial tracings obtained from these twelve patients with acute coronary thrombosis were reviewed, several striking features presented themselves. There was an unusual similarity in the tracings of a good many of the cases, both in the changes and in the speed of progression of the changes. The tracings of several patients were almost exact mirror images of some others (if the isoelectric line were considered the mirror). In short, the electrocardiograms permitted an easy and satisfactory grouping of the serial changes in Lead IV following acute coronary thrombosis into three types.

There is one which we shall call for convenience' sake the deeply negative  $T_4$  (or "posterior") type in which the earliest change (the first day or so after infarction) is marked elevation of the RS-T segment (Figs. 1 and 2). Within the next few days the RS-T elevation becomes less marked and rapidly tends to approach the isoelectric line. Concomitantly with this is a sharp inversion of the T-wave. Often  $Q_4$  becomes increasingly deep and  $R_4$  decreases in size. Within the next few weeks large inverted T-waves are seen from 10 to 25 mm. in depth; they are often cove-planed in this period and of the "coronary" type.<sup>3b</sup> During the next few weeks the T-wave tends to become smaller and more normal appearing. After about two months there is not much in Lead IV indicative of the infarction except perhaps a very deep  $Q_4$  with an abnormally small  $R_4$ , or a deeply inverted  $T_4$ . This type, with original elevation of RS- $T_4$  and later negative  $T_4$ , is associated with similar RS-T elevations and inversion of the T-waves in Leads II and III. Barnes and Whitten have shown that this " $T_3$  type" of electrocardiogram indicates infarction of the posterior basal portion of the left ventricle or of the interventricular septum.<sup>16, 17a</sup> The progressive changes in Lead IV outlined above then are to be ascribed to posterior infarction, justifying the name "posterior type of serial change."

The progressive changes in Lead IV of the second group (Figs. 3 and 4), the positive  $T_4$  (or "anterior") type, have characteristics almost exactly opposite to the first. The earliest changes are marked depression of the RS-T segment with a T-wave which very soon becomes positive. As the T-wave grows taller and more positive the RS-T de-

pression becomes less noticeable. Concomitantly there is almost always either a complete loss of the  $Q_4$  deflection, or at least a marked diminution in its size. For the next few weeks the T-wave is likely to be

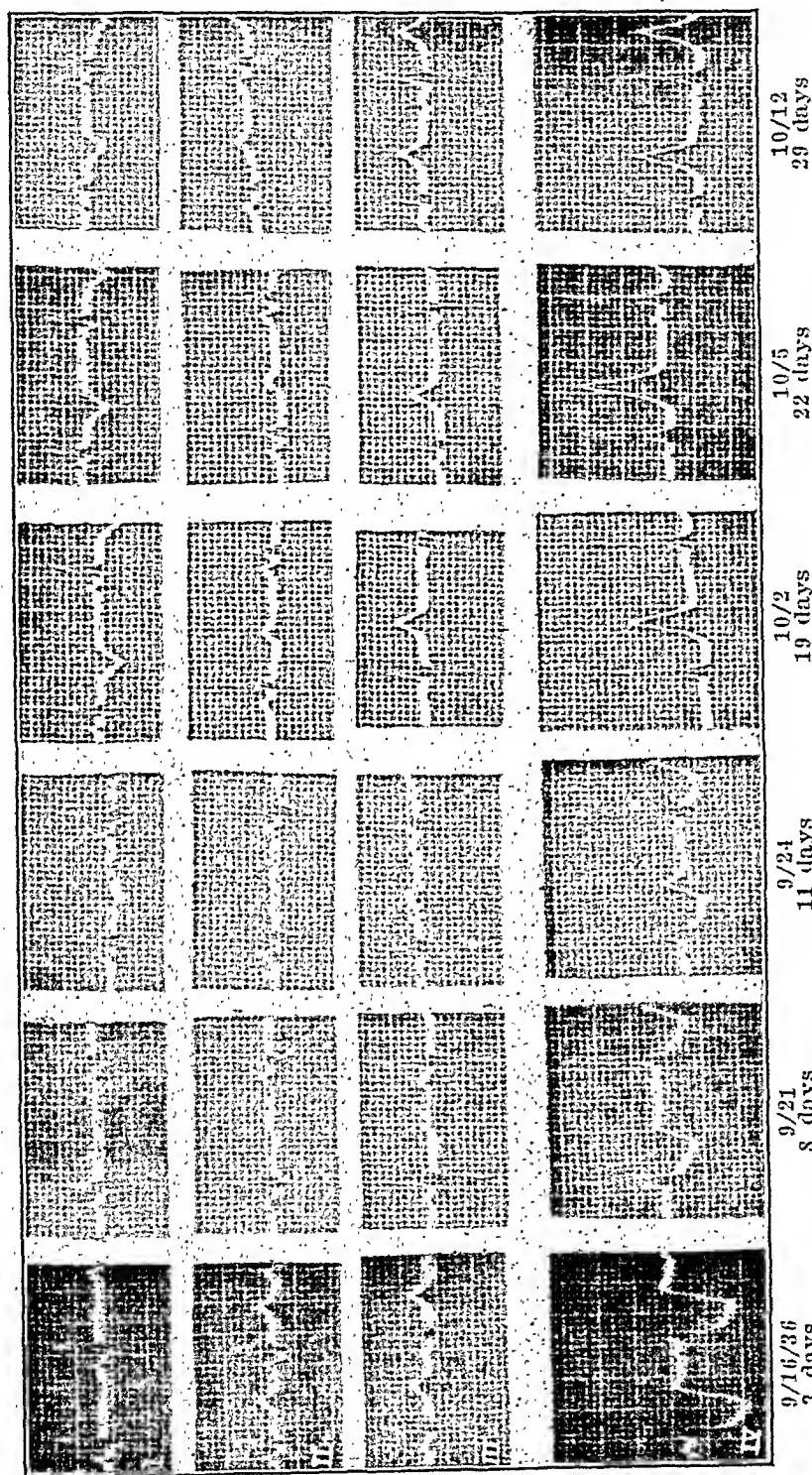


FIG. 3.—Anterior Infarction. E. B., No. 86585, male, aged sixty-three years. The first tracing (September 16) was taken three days after a single attack of persistent, dull, substernal burning. While the conventional leads show only a flat T-wave in Lead I with a suggestion of a  $Q_1$  wave, the RS-T segment in Lead IV is strikingly depressed. As this RS-T depression becomes less prominent, the T-wave becomes constantly more positive.  $Q_4$  is absent throughout. The upright  $T_1$  waves are unusually tall (even higher than the QRS on October 5), and indicate the presence of an active cardiac process. The tall T-wave. The conventional leads in this final (permanent) picture is apt to be an absent  $Q_4$  wave and positive  $T_1$  wave. The conventional leads in this case also show serial changes (inversion of  $T_1$ ); these changes at first are not as marked in Lead I as in Lead IV and are not as characteristic of acute coronary thrombosis. In Lead IV the serial changes fit nicely into the "anterior infarct" pattern from the start.

unusually tall, and although positive it has the same coved appearance which characterizes the inverted coronary T-wave of Pardee, an observation recently stressed by Wolferth and Wood.<sup>15, 6c</sup> The T-wave later becomes smaller. The changes in Lead IV in this group of cases tend to be more permanent—so that for months and even years many

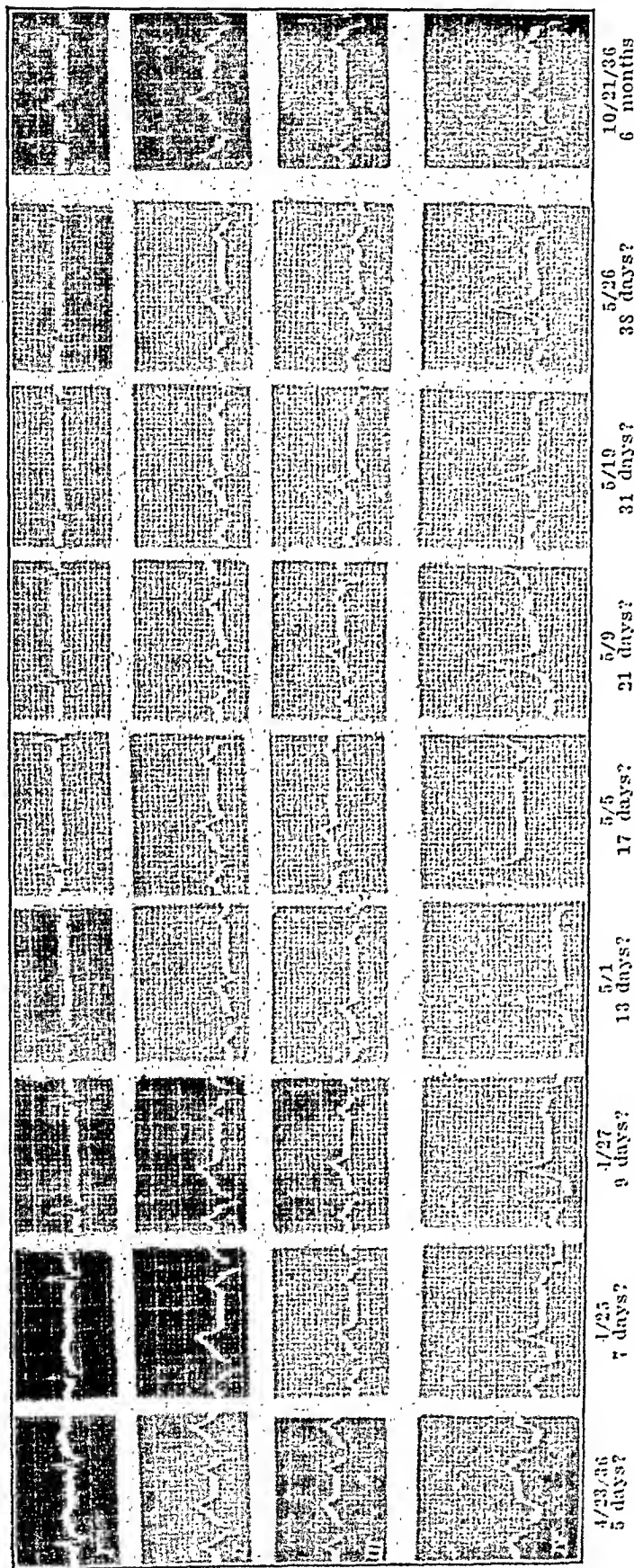


Fig. 4.—Anterior infarction. S. B., No. 82307, male, aged forty-eight years. The patient had several attacks of epigastric pain related to exertion for one month before admission. An unusually severe seizure with radiation of the pain to the interscapular region occurred five days before, and to a lesser degree the day of admission. The first electrocardiogram taken five days after the severe attack is practically normal in the conventional leads (except for deep  $Q_1$ ), but shows a marked depression of the RS-T interval in Lead IV. The T-wave cannot be made out clearly. The next electrocardiogram shows RS-T<sub>4</sub> less depressed but T<sub>1</sub> is upright and pointed. As the RS-T segment comes up to the normal level the T-wave becomes taller and more positive. Note that  $Q_4$  is practically absent in all of these tracings, and that on May 5 the high pardee T-waves in the conventional leads. The very tall positive T-waves have the same characteristics as the deeply coved, inverted, pardee T-waves in the conventional leads. They correspond in this case to the clinically active phase of the infarction (as determined by physical findings, while blood cell count, sedimentation rate, and blood pressure). The tall T-wave soon becomes smaller and less characteristic so that the final picture (taken six months after the infarction, i.e., October 21) is that of a small  $Q_1$  with a normally shaped but upright T<sub>1</sub>. It is to be stressed in this case that Lead I shows only minimal serial changes characteristic of anterior infarction, while Lead IV shows grosser and more characteristic serial changes.

cases show the typical picture of infarction of this type—an absent  $Q_4$ -wave and positive  $T_4$ . The changes in Lead IV described for this group are often associated with RS-T elevation and T inversion in Lead I. This  $T_1$  change, when characteristic, has been found to indicate infarction of the anterior apical portion of the left ventricle or the interventricular septum.<sup>16, 17a, d</sup> The serial changes in Lead IV which have been described in this paragraph as of the “anterior” type are due then to anterior apical infarction.

Of our twelve cases, four showed typical “posterior” type, and four “anterior” type of serial change. Those remaining form a third group of cases (the “indeterminate” type) in which the serial changes in the fourth lead are not characteristic or striking enough to permit easy classification as either one of the two main types outlined above. The cause for this lack of conformance to a definite “anterior” or “posterior” type, such as the presence of multiple infarcts, or the additive effects of old and recent infarction, is discussed later. In these patients the serial changes in the conventional leads are also not striking or characteristic of coronary infarction. In any case, however, the serial changes in this “indeterminate” type, although not fitting into the two main, typical electrocardiographic patterns described above, are marked enough to indicate clearly that an active process is present in the heart. By correlation with the clinical findings we are relatively certain that these changes are due to coronary infarction.

#### COMMENT

Since all the patients here reported recovered from their cardiac attack, it is not possible to state with accuracy just what pathological process occurred in each case to give the electrocardiographic changes recorded. Our experience with the autopsy findings in cases of coronary thrombosis coincides, however, in the main with those of Parkinson and Bedford, Barnes and Whitten, and Wolferth, who find that a typical  $Q_3T_3$  type of electrocardiogram such as is shown in Figs. 1 and 2 is practically pathognomonic of an infarction in the posterior basal portion of the left ventricle or interventricular septum. Although lacking absolute proof, we are relatively certain that the serial changes shown in these figures are due to posterior infarction. The same considerations hold true for the QRS, RS-T, and T changes in the first lead in Figs. 3 and 4, which indicate an anterior infarction. It is of interest to note how reciprocal the registrations of anterior and posterior infarcts are in the chest lead. Fig. 1 (posterior infarct) is almost exactly the reciprocal to Fig. 3 (anterior infarct). This distinction is fundamental.

It has been stated by Barnes and Whitten, Wolferth and Wood, Wilson, and others that the fourth lead does not register posterior

infarction as well as it does anterior. We believe this view is largely due to the fact that tracings were not taken early enough after the infarction. Thus in Figs. 1 and 2 the RS-T segment deviation is even more marked in Lead IV than in any other lead, and compares with the deviation shown by the anterior infarct in Figs. 3 and 4. A study of Lead IV in Figs. 1 and 2 shows that the marked RS-T elevation after posterior infarction usually lasts only a few days. The later changes are largely those of increasing depth of the inverted T-wave. During this interval of several days between the appearance of the markedly elevated RS-T segment and the markedly inverted  $T_4$  the fourth lead may look fairly normal (Figs. 1 and 2). The lack of early and frequent tracings may then be the reason for the alleged failure of Lead IV to register posterior infarction. Several days later Lead IV shows such marked serial changes (in the increasingly deep T-wave) that the diagnosis becomes much more apparent. This indicates the necessity of obtaining early and frequent electrocardiograms on patients with possible coronary infarction. It is advisable to take the first tracing as soon after the attack as possible; then daily for the first week; then biweekly for the first month or so if there is any doubt as to the clinical or electrocardiographic diagnosis, so that a final evaluation on sufficient grounds can be made.

The fact that the T-wave is normally inverted in Lead IV and that deep negative T-waves, as large as 15 mm., have been reported in normal individuals<sup>14</sup> makes it more difficult to recognize posterior than anterior infarction in this lead after the first few days of marked RS-T deviation are over. Of great help at this time is a *correlative* study of the  $QRS_4$  and  $T_4$  complexes. In a normal individual, when  $T_4$  is deep,  $QRS_4$  is also large (25 to 40 mm.). In posterior infarction, on the other hand, a deep  $T_4$  (10 to 20 mm.) is often associated with a relatively low QRS (Figs. 1 and 2). In fact, QRS is sometimes smaller even than  $T_4$ , and is often slurred.

It is to be noted that the serial changes in Lead IV after coronary thrombosis (no matter which type) can be conveniently grouped as early, midperiod, or late, depending upon how soon after the infarction these changes are likely to appear. We can classify the RS-T deviations and the changes in the initial ventricular complex (absence of  $Q_4$ , or absence of  $R_4$ ) as early, making their appearance the first few days. The tall, sharply peaked T-waves are generally characteristic of the midperiod (first to third week); while the late changes seen even months after the infarction are almost exclusively in the ventricular complex—in anterior infarction it is the small or absent  $Q_4$  and positive  $T_4$ ; in posterior infarction it is the very deep  $Q_4$ , or the negative  $T_4$  which is disproportionately deep in comparison with the small QRS.

Both the T and QRS changes following coronary thrombosis may be transient. Of these the T changes are often the only ones seen in mild cases, and are more likely to be ephemeral; while the QRS changes are usually more permanent.

The large positive or negative  $T_4$  waves usually last only a few weeks and appear to be clinically associated with activity of the cardiac process.<sup>15</sup> The treatment that a patient with coronary thrombosis receives is, of course, determined largely by his clinical course; still it is probably wise to consider the process an active one while the  $T_4$  waves are changing rapidly, and to keep the patient at rest.

Aside from the fact that, in general, posterior infarction is known to have a better prognosis than anterior infarction, it appears that those cases which show the characteristic, striking, rapidly changing electrocardiogram in Lead IV (and the conventional leads) fare better clinically than those showing less marked, slower, and less typical electrocardiographic changes. This is probably based on the fact that extensive single infarcts or multiple infarcts involving both the anterior and posterior walls of the left ventricle give electrocardiographic changes which tend to be reciprocal, and balance each other. There are cases (as in Fig. 4) in which the serial changes in the conventional leads are not marked and do not fit easily into a characteristic pattern, but in which the Lead IV changes are prominent and typical. The conformity to type in these cases indicated a favorable prognosis, which the clinical course amply confirmed.

It should be stressed in closing that a familiarity with the serial changes in the fourth as well as in the conventional leads is often of use in confirming a diagnosis of infarction suggested by a single electrocardiogram. In some cases, particularly in anterior infarction, the conventional leads at first were within normal limits, while Lead IV was already definitely suggestive of anterior infarction (Fig. 4). Furthermore, the serial changes in the conventional leads were minimal, while in the fourth lead they were marked and fitted into a characteristic pattern of anterior infarction. In some other cases, as in Figs. 5 and 6, the progressive changes are only slight in the conventional leads and are not as confirmatory of the clinical impression of coronary thrombosis as is Lead IV, where the changes fit into a more diagnostically typical pattern. These considerations form the basis for the use of serial four-lead electrocardiographic studies in the confirmation of the clinical diagnosis of coronary occlusion.

#### SUMMARY AND CONCLUSIONS

1. Frequent serial four-lead electrocardiograms were obtained on twelve patients with the clinical diagnosis of acute coronary thrombosis. The serial changes in the precordial lead permitted ready group-



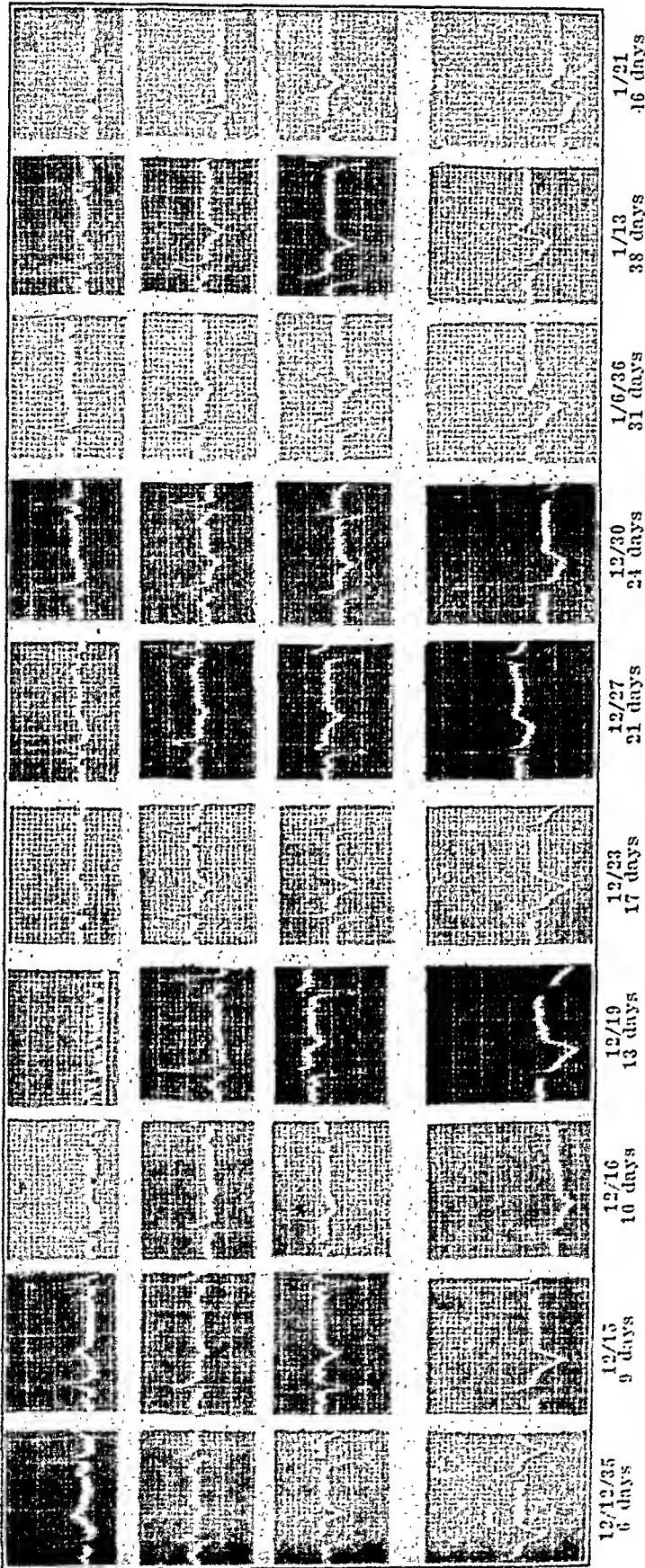


FIG. 5.—Indeterminate type. B. K., No. 78904, male, aged forty-nine years. The patient had a two-year history of precordial pain and dyspnea on exertion. Four days prior to admission he experienced severe pain in the precordium radiating to the left shoulder. The first electrocardiogram taken six days after his attack is of the QsT<sub>1</sub> type. The RS-T segment in Lead IV is slightly elevated (which is significant). The changes for the next three days (December 15) are the usual predictable serial changes after posterior infarction. On December 16, however, Lead IV shows a sudden turn. Overnight the Q<sub>i</sub> becomes unusually small and remains so. After this the Lead IV serial changes no longer follow the typical pattern of posterior infarction as in Figs. 1 and 2, but begin to show T<sub>i</sub> waves that are biphasic, and finally more positive than negative. On the very day that Q<sub>i</sub> disappeared (December 16) the patient had a recurrence of severe substernal pain, fall in blood pressure, and collapse. Clinically a new coronary closure was postulated. The sudden turn in serial changes on December 16 from the "posterior" to the "anterior" infarct type helped substantiate this conclusion.

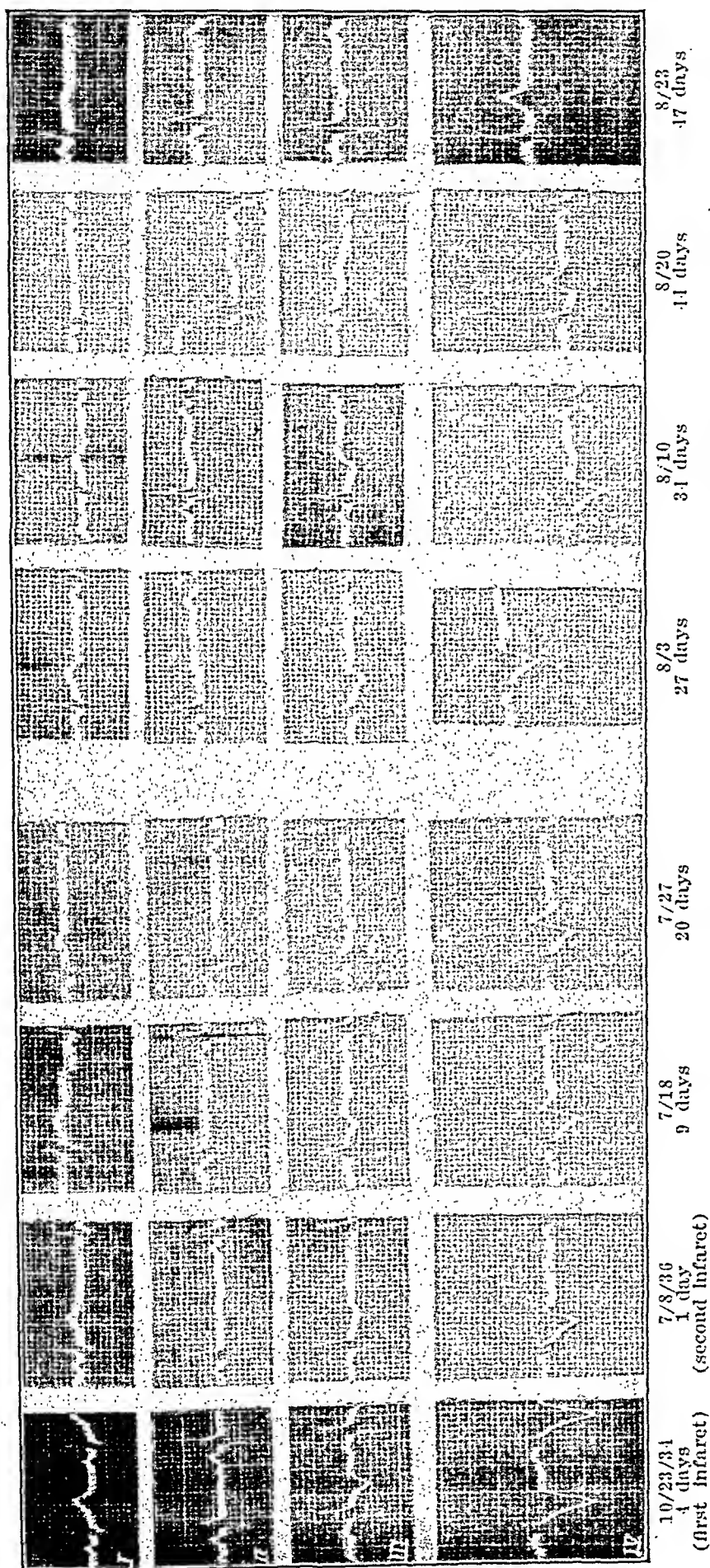


FIG. 6.—Indeterminate type. M. G., No. 68062, male, aged thirty-eight years. Patient was first admitted Oct. 21, 1934, with precordial pain radiating to the left shoulder for two days. The first electrocardiogram taken shows the typical Q-Ts type of change found in posterior infarction. He was readmitted June 14, 1935, with severe precordial pains lasting twelve hours. There was no clinical evidence of a new closure. The serial four-lead electrocardiograms showed no progressive changes and were typical of the posterior infarct type. He was readmitted July 8, 1936, with an attack of precordial pain lasting three hours. He showed clinical evidence of a new closure (fever and fall in blood pressure) and the electrocardiograms (July 8 to Aug. 23, 1936) show serial changes. In the conventional leads they are not prominent, but in Lead IV the inverted T-wave distinctly changes to a diphase T, which finally (August 23) is entirely upright. Notice that with the second infarction (from the second to the eighth tracing of this figure) the patient shows an "indeterminate type of serial change" in Lead IV, while the first infarction was typically of the "posterior" T<sub>3</sub> type. This often occurs with successive infarctions and was shown by two other cases of the series studied.



ing into three types, the "anterior infarct" type (4 cases), the "posterior infarct" type (4 cases), and the "indeterminate" type (4 cases).

2. Anterior infarction causes serial changes in the chest lead almost exactly opposite to those produced by posterior infarction. In anterior infarction the RS-T segment is at first depressed. As this returns to normal the Q-wave becomes smaller and the T-wave more upright. Soon the classical picture of anterior infarction is shown; absent  $Q_4$ , and upright, coved T-wave. Posterior infarction shows at first a markedly elevated RS-T segment in Lead IV. As this returns to normal,  $Q_4$  becomes large, and  $T_4$  is unusually deeply inverted.

3. As in the conventional leads, the RS-T segment changes are likely to be the earliest ones; the markedly coved, sharply peaked or tall T-waves are more characteristic of the midperiod (the first 3 to 4 weeks). The changes which characterize the late stage of coronary thrombosis and which appear to be permanent in a good many cases are the abnormal form of the QRS and the direction of the T-wave. The change in  $Q_4$  (either very deep in posterior infarct or absent in anterior infarct) is often among the first to appear and the last to disappear. Three or four months after the coronary infarction there is little serial change in Lead IV.

4. If electrocardiograms are taken early enough, the presence of a posterior infarct is registered as surely in the fourth lead as an anterior.

5. One should view with suspicion a precordial electrocardiogram which corresponds to any of the tracings published here, for they represent the many changes possible after coronary thrombosis. Particular emphasis is laid on any tracing showing an elevated RS-T segment or a disproportionately deep negative  $T_4$  wave (often seen in posterior infarction).

6. Occasionally a patient will not demonstrate a characteristic pattern of serial changes in the conventional leads and will do so in the chest lead. The fact that the fourth lead serial changes fit into a definite pattern not only helps substantiate the diagnosis of coronary infarction but often permits localization of the infarct.

7. A knowledge of the expected serial changes in the four-lead electrocardiogram is useful in making the differential diagnosis between a second infarction and a simple anginal attack after the original infarction. In the latter there will be no interruption in the sequence of the serial changes due to the original infarction. If a new occlusion occurred, however, the sequence will be interrupted by new findings prominent in all leads, especially the fourth.

8. Cases of coronary thrombosis which give electrocardiographic changes fitting easily into the classical types described above seem to

have better prognoses than the indeterminate type with small, slowly developing, atypical changes. This may be because the infarction is single and not large.

We are extremely indebted to Dr. I. W. Held and Dr. A. A. Epstein on whose medical services these patients were studied, and to Dr. H. Vesell for the cordial cooperation of the electrocardiographic department in this work.

## REFERENCES

1. Smith, F. M.: (a) The Ligation of Coronary Arteries With Electrocardiographic Studies, *Arch. Int. Med.* 22: 8, 1918.  
(b) Further Observations on the T-Wave of the Electrocardiogram of the Dog Following Ligation of the Coronary Arteries, *Arch. Int. Med.* 25: 673, 1920.
2. Herrick, J. B.: Thrombosis of the Coronary Arteries, *J. A. M. A.* 72: 387, 1919.
3. Pardee, H. E. B.: (a) An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* 26: 244, 1920.  
(b) Heart Disease and Abnormal Electrocardiograms, With Special Reference to the Coronary T-Wave, *Am. J. M. Sc.* 169: 270, 1925.
4. Cooksey, W. B., and Freund, H. A.: Serial Electrocardiographic Studies in Coronary Thrombosis, *AM. HEART J.* 6: 608, 1931.
5. Sigler, L. H.: Acute Coronary Occlusion. A Clinical and Electrocardiographic Study of Twenty Cases, *Ann. Int. Med.* 4: 969, 1931.
6. Wolferth, C. C., and Wood, F. C.: (a) Electrocardiographic Diagnosis of Coronary Occlusion by Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.  
(b) Further Observations Upon the Use of Chest Leads in the Electrocardiographic Study of Coronary Occlusion, *M. Clin. North America* 16: 161, 1932.  
(c) The Electrocardiographic Diagnosis of Cardiac Infarction. In *Modern Concepts of Cardiovascular Disease*, published by the American Heart Association, IV, No. 5, May, 1935.
7. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surface, *AM. HEART J.* 5: 599, 1930.
8. Lieberman, A., and Liberson, F.: The Value of the Posterior-Anterior Chest Lead in Cardiac Diagnosis, *Ann. Int. Med.* 6: 1315, 1933.
9. Hoffman, A. M., and Delong, E.: Standardization of Chest Leads and Their Value in Coronary Thrombosis and Myocardial Damage, *Arch. Int. Med.* 51: 947, 1933.
10. Katz, L. N., and Kissin, M.: A Study of Lead IV. Its Appearance Normally, in Myocardial Disease, and in Recent Coronary Artery Occlusion, *AM. HEART J.* 8: 595, 1933.
11. Goldbloom, A. A.: Clinical Evaluation of Lead IV, *Am. J. M. Sc.* 187: 489, 1934.
12. Master, A. M.: The Precordial Lead in 104 Normal Adults, *AM. HEART J.* 9: 511, 1934.
13. Richter, H. A.: Value of Serial Electrocardiograms in Coronary Thrombosis, *Am. J. M. Sc.* 189: 487, 1935.
14. Bohning, A., and Katz, L. N.: The Four-Lead Electrocardiogram in Coronary Sclerosis, *Am. J. M. Sc.* 189: 833, 1935.
15. Wood, F. C., and Wolferth, C. C.: Huge T-Waves in Precordial Leads in Cardiac Infarction, *AM. HEART J.* 9: 706, 1934.
16. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, *AM. HEART J.* 5: 142, 1929.
17. Barnes, A. R.: (a) Electrocardiographic Localization of Myocardial Infarcts, *M. Clin. North America* 14: 671, 1930.  
(b) Correlation of Initial Deflections of Ventricular Complex With Situation of Acute Myocardial Infarction, *AM. HEART J.* 9: 728, 1934.  
(c) Q and T Types of Electrocardiograms: Their Comparative and Complementary Value in Indicating Occurrence of Acute Myocardial Infarction, *AM. HEART J.* 9: 722, 1934.  
(d) Electrocardiogram in Myocardial Infarction, *Arch. Int. Med.* 55: 457, 1935.

## THE DURATION OF SYSTOLE IN HYPOCALCEMIA\*

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THE purpose of this paper is to report observations on the duration of "electrical systole" as measured by the Q-T interval of the electrocardiogram, and of "mechanical systole" as measured in records of the heart sounds in the presence of abnormally low blood serum calcium content. It has previously been reported that the Q-T interval of the electrocardiogram is prolonged when the serum calcium is low.

In 1922 Carter and Andrus<sup>1</sup> described prolonged Q-T intervals in six patients with infantile tetany and in three patients with adult tetany, all with low serum calcium values. One of the adult patients had been taking large amounts of sodium bicarbonate, another had pyloric obstruction, while the third had tetany of undetermined origin. In all instances the Q-T interval became shorter as the serum calcium rose in response to treatment.

In 1929 White and Mudd<sup>2</sup> reported prolonged Q-T intervals in two patients with tetany and low serum calcium, and a shortened Q-T interval in one patient with elevated serum calcium. The Q-T intervals returned to normal as the serum calcium values were restored to normal. One other case had normal Q-T intervals, both when the serum calcium was elevated and when it was normal. In one out of five patients with uremia the Q-T interval was prolonged. Systole was not prolonged in patients with hypertension.

In 1932 Spalding's observations were reported by Ballin.<sup>3</sup> He observed that in tetany following thyroidectomy the Q-T interval was prolonged, but that it returned to normal after successful parathyroid transplant. Furthermore, in hyperparathyroidism the Q-T interval was shortened, but returned to normal following parathyroidectomy.

In 1936 Kellog and Kerr<sup>4</sup> reported two patients with hyperparathyroidism and hyperealcemia in which the Q-T intervals were shortened. After operation the serum calcium dropped to normal and the Q-T intervals rose to normal. The shortening of the Q-T intervals was not considered to be sufficiently pronounced to be of value in the clinical diagnosis of hyperparathyroidism.

It has long been known<sup>5-14</sup> that the duration of ventricular systole is related to the heart rate. A number of formulas have been devised to express this relationship. One of the most satisfactory of these

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This study was assisted by a grant to Dr. Frank N. Wilson from the Horace H. Rackham Endowment Fund.

formulae is Bazett's,<sup>7</sup>  $\text{systole} = K \sqrt{\text{cycle}}$ . In normal men K was found to vary between 0.342 and 0.392, with an average value of 0.368. In normal women K varied between 0.36 and 0.44, with an average value of 0.399. In our observations we have applied Bazett's formula and have used K as an expression of the duration of systole, thus taking into account the effects of variations in heart rate.

We have recently observed nine patients with abnormally low serum calcium values and abnormally prolonged ventricular systole as measured from the beginning of the Q-wave to the end of the T-wave of the standard electrocardiogram. The essential data are given in Table I.

TABLE I

THE DURATION OF SYSTOLE AS MEASURED IN ELECTROCARDIOGRAMS AND HEART SOUND RECORDS, EXPRESSED IN SECONDS, AND THE CALCIUM AND INORGANIC PHOSPHORUS VALUES OF THE BLOOD SERUM, EXPRESSED IN MG. PER 100 C.C.

CASE	SEX	DIAGNOSIS	ELECTROCARDIOGRAM				BLOOD		
			DATE	SYSTOLE	CYCLE	K (BAZETT'S FORMULA)	DATE	SERUM CA.	SERUM PHOS.
1	F	Hypoparathyroidism	2/18/35	0.47	0.745	0.545	2/16/35	7.8	6.1
			2/19/35	0.46	0.82	0.508			
				0.32	0.815	0.355*			
			2/27/35	0.52	0.85	0.565			
			2/28/35	0.50	0.78	0.567	2/28/36	9.4	5.2
			2/29/36	0.40	0.94	0.413			
2	F	Hypoparathyroidism	1/28/36	0.40	0.77	0.456	1/28/36	7.3	6.6
			2/29/36	0.425	0.745	0.493	2/29/36	6.2	7.0
				0.36	0.752	0.415*			
			3/17/36	0.40	0.83	0.440	3/17/36	8.3	5.6
3	F	Hypoparathyroidism	3/28/36	0.48	0.84	0.524	3/27/36	5.1	6.5
			3/31/36	0.52	0.985	0.525			
				0.37	0.98	0.375*			
			4/ 1/36	0.43	0.745	0.499	4/ 1/36	6.9	4.8
			4/ 4/36	0.43	0.80	0.481	4/ 4/36	7.7	
			4/ 9/36	0.44	0.88	0.469	4 /9/36	8.4	4.8
4	M	Chronic nephritis, hypertension, uremia	4/13/36	0.40	0.56	0.535	4/15/36	6.0	12.7
			4/16/36	0.43	0.61	0.551			
				0.266	0.60	0.344*	4/17/36	6.7	12.5
5	M	Subacute nephritis, hypertension, uremia	2/26/36	0.46	0.80	0.514	2/26/36	5.2	9.9
			2/27/36	0.535	0.842	0.583	2/27/36	4.8	10.5
				0.335	0.84	0.366*			
6	M	Urethral stricture, chronic pyelonephritis, uremia	2/14/36	0.52	0.83	0.571	2/20/36	6.3	8.2
			2/18/36	0.535	1.03	0.527			
				0.34	1.025	0.336*	2/26/36	6.5	
7	M	Chronic nephritis, hypertension, uremia	5/26/36	0.36	0.66	0.443	5/26/36	8.5	8.4
8	F	Subacute nephritis, hypertension, uremia	5/ 4/36	0.37	0.62	0.471	5/ 5/36	5.2	13.1
9	F	Chronic nephritis, hypertension, uremia	5/ 6/36	0.38	0.66	0.468	5/20/36	7.6	10.0
			5/21/36	0.34	0.61	0.436			

\*Mechanical systole as measured in heart sound records.

Three of these patients were women who had hypoparathyroidism and tetany following subtotal thyroidectomy.\* In them the response to treatment could be followed sufficiently closely to demonstrate that as the serum calcium rose to normal the duration of systole became shorter (Fig. 1).

The other six patients had nephritis with renal failure and uremia, accompanied by abnormally low serum calcium values. Their electro-

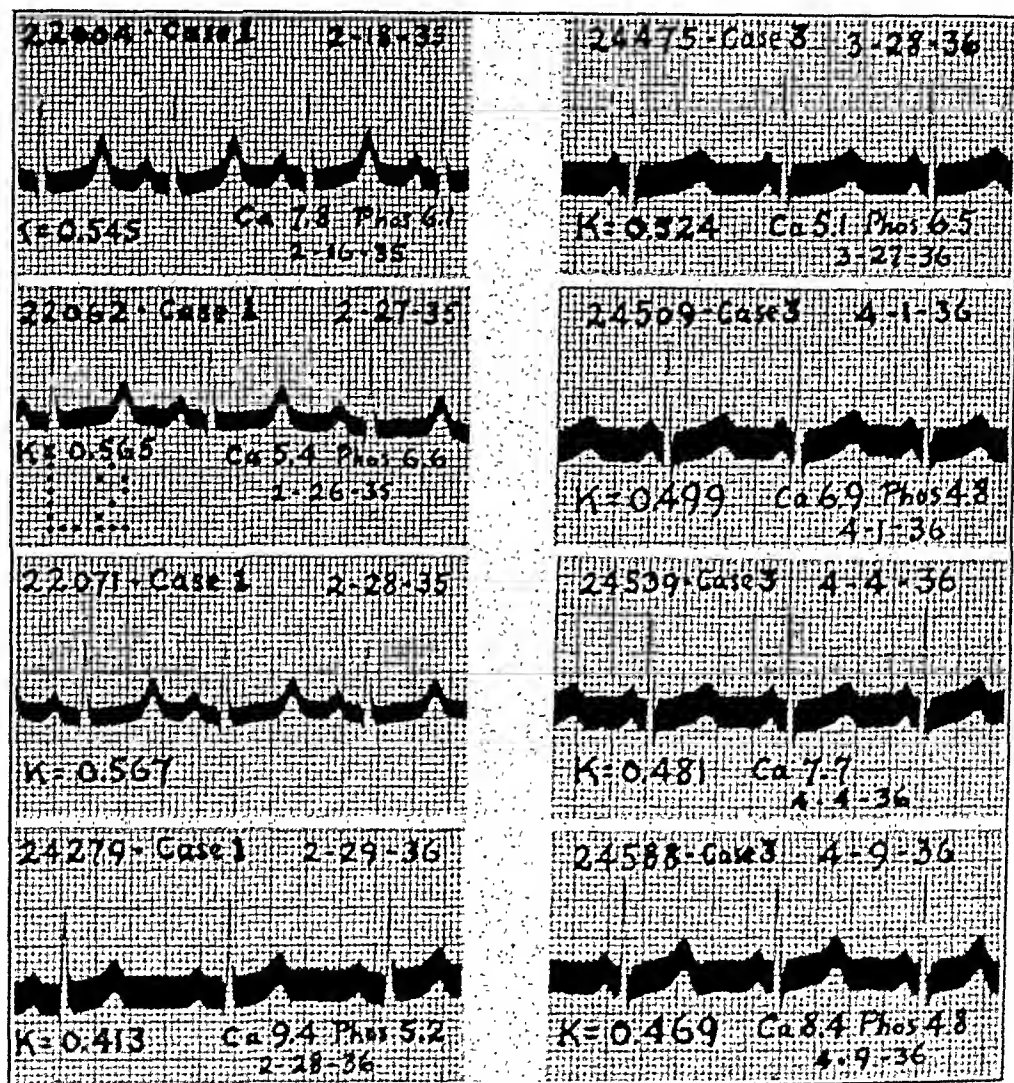


Fig. 1.—Four electrocardiograms, Lead II, of each of two women with hypoparathyroidism following subtotal thyroidectomy. The dates of the curves are given, also the blood serum calcium and phosphorus values in milligrams per 100 c.c., and the dates upon which these determinations were carried out.  $K$  is the index of the duration of systole as determined from Bazett's formula,  $\text{systole} = K\sqrt{\text{cycle}}$ .

cardiograms showed prolonged Q-T intervals (Fig. 2). They did not live long and it was not possible to observe variations in systole as re-

\*Clinical observations and studies of calcium and phosphorus metabolism in two of these patients have been reported by Freyberg, R. H., Grant, R. L., and Robb, M. A. (Hypoparathyroidism, J. A. M. A. 107: 1769, 1939). Their cases 1 and 2 are our cases 2 and 1, respectively.

lated to changes in the serum calcium content. All six of these patients had hypertension. In several of them it was thought, upon admission to the hospital, that hypertensive heart disease was the chief disease from which they were suffering. The electrocardiograms, however, showed such striking prolongation of the Q-T interval as to suggest hypocalcemia. This led to a study of the renal function, and to the discovery of renal failure as the most important condition present. The prolonged Q-T interval may be of diagnostic importance in the recognition of otherwise unsuspected conditions associated with low calcium values.

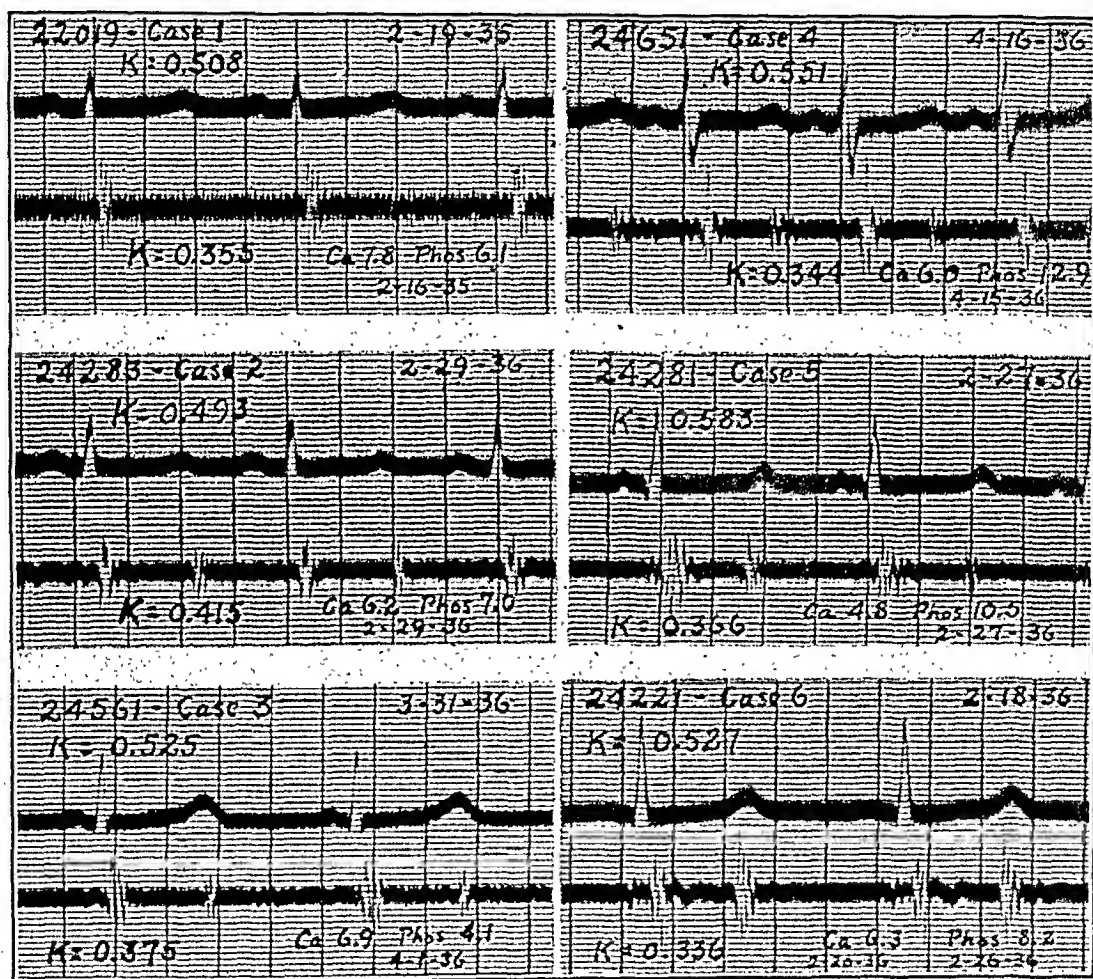


Fig. 2.—Simultaneous electrocardiograms, Lead I, and heart sound records of three patients with hypoparathyroidism, first column, and three patients with nephritis and uremia, second column. The dates of the curves and of the determinations of the blood serum calcium and phosphorus determinations are given. K is the index of the duration of systole as determined for the electrocardiograms and the sound records from Bazett's formula.

In the three cases of hypoparathyroidism and in three of the cases of nephritis, the heart sounds were recorded simultaneously with the electrocardiogram (Fig. 2). It was found that the duration of systole, as measured from the beginning of the first sound to the beginning of the second sound, was normal. Bartos and Burstein<sup>11</sup> reported in 1924 that in normal men mechanical systole is about 3 to 5 per cent shorter

than electrical systole, as measured respectively in heart sound records and in electrocardiograms. They also found that during altered conditions of the circulation mechanical and electrical systole usually, but by no means always, changed in the same direction, but only rarely to equal degree. In these patients with hypocalcemia, K was from 15 to 37 per cent less for mechanical systole than for electrical systole. In several normal individuals in whom we recorded electrocardiograms and heart sounds simultaneously, K was from 3 to 8 per cent less for mechanical systole than for electrical systole. In one instance it was 3 per cent greater for mechanical than for electrical systole.

#### SUMMARY

The Q-T interval of the electrocardiogram is abnormally prolonged in the presence of abnormally low blood serum calcium levels. This may be very striking, and may be of diagnostic value in the recognition of otherwise unsuspected conditions associated with hypocalcemia. The duration of mechanical systole, as measured in heart sound records, is not prolonged in hypocalcemia.

#### REFERENCES

1. Carter, E. P., and Andrus, E. C.: The Q-T Interval in the Human Electrocardiogram in the Absence of Cardiac Disease, *Trans. Am. Soc. Clin. Invest.*, J. A. M. A. 78: 1922, 1922.
2. White, P. D., and Mudd, S. G.: Observations on the Effect of Various Factors on the Duration of the Electrical Systole of the Heart as Indicated by the Length of the Q-T Interval of the Electrocardiogram, *J. Clin. Investigation* 7: 387, 1929.
3. Ballin, M.: Parathyroidism, *Ann. Surg.* 96: 649, 1932.
4. Kellog, F., and Kerr, W. J.: Electrocardiographic Changes in Hyperparathyroidism, *AM. HEART J.* 12: 346, 1936.
5. Garrod, A. H.: On the Relative Duration of the Component Parts of the Radial Sphygmograph Trace in Health, *Proc. Roy. Soc.* 18: 351, 1870.
6. Meakins, J.: Prolongation of the S-T Interval of the Ventricular Complex as Shown by the Electrocardiograph, *Arch. Int. Med.* 24: 489, 1919.
7. Bazett, H. C.: An Analysis of the Time Relations of Electrocardiograms, *Heart* 7: 353, 1920.
8. Katz, L. N.: Factors Modifying the Duration of Ventricular Systole, *J. Lab. and Clin. Med.* 6: 291, 1921.
9. Buchanan, J. A.: A Study of the S-T Interval in One Thousand and Twenty-Eight Electrocardiograms, *Arch. Int. Med.* 28: 484, 1921.
10. Fenn, G. K.: Studies in the Variation of the Q-R-S-T Interval, *Arch. Int. Med.* 29: 441, 1922.
11. Bartos, E., and Burstein, J.: Can Variations in Ventricular Systole Be Determined From Electrocardiogram Deflections? *J. Lab. and Clin. Med.* 9: 217, 1924.
12. Lombard, W. P., and Cope, O. M.: The Duration of the Systole of the Left Ventricle of Man, *Am. J. Physiol.* 78: 263, 1926.
13. Cheer, S. N., and Li, R. C.: Studies on the Electrical Systole (Q-T Interval) of the Heart. 1. The Duration of Electrical Systole in Normal Chinese, *Chinese J. Physiol.* 4: 191, 1930.
14. Adams, W.: The Normal Duration of the Electrocardiographic Ventricular Complex, *J. Clin. Investigation* 15: 335, 1936.



# THE POSTURAL EFFECTS ON BLOOD PRESSURE FOLLOWING INTERRUPTION OF THE VASOMOTOR NERVES OF MAN\*

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**B**LOOD pressure is maintained by the minute output from the heart, the volume of blood, the elasticity of the blood vessels, and the peripheral resistance. Under normal conditions the quantity of blood remains the same for fairly long periods of time; elasticity of the blood vessels is a minor factor and is associated with the peripheral resistance. Blood pressure, as a result, is more closely dependent on the energy of the heart and the peripheral resistance. These conditions are controlled by nervous, chemical, and mechanical factors which interact to maintain blood pressure at a constant level. The nervous control, or vasomotor mechanism, includes an efferent portion, associated with the peripheral vascular system, which regulates the size of the peripheral vascular bed. This is under control of a central mechanism. The efferent portion has its effect, for the most part, on the arterial side of the circulation, more precisely on the arterioles rather than on the larger arteries.

The vasomotor nerves to the splanchnic region control the greater portion of the blood vessels of the abdominal viscera. Inasmuch as a large part of the total blood in the body is contained in this region, in animals the general arterial blood pressure is more markedly altered by section of the splanchnic nerves than by section of any other nerves in the body. In man, an upright animal, in the change from the horizontal to the upright position, the splanchnic nerves should, no doubt, play a predominant rôle in the maintenance of blood pressure.

I desired to determine what happens to blood pressure and pulse rate when voluntary change from the recumbent to the upright posture was made by persons whose splanchnic nerves had been interrupted. The following types of men or women were studied: (1) as controls, those whose condition was normal; (2) also as controls, those whose blood pressure and pulse rate were normal before operation but whose vasomotor pathways to the abdominal viscera had been interrupted for postcholecystectomy pain or megacolon; (3) those whose vasomotor pathways to the abdominal viscera had been interrupted because of hypertension. In addition, the response in the vasomotor system following the operations referred to in the foregoing sentences resembles the vaso-

\*Abridgment of thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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motor response of patients who have orthostatic hypotension. For comparison, therefore, it was considered desirable to record the change in blood pressure and pulse rates of patients who had orthostatic hypotension when they voluntarily changed from the recumbent to the upright posture.

The concept underlying the work was accepted as worthy of investigation by the late Dr. G. E. Brown when it was still in the realm of speculation. The investigation was pursued with his cooperation and with that of Doctors Adson, Craig, Mann, Essex and Allen.

### METHODS

A standard mercury manometer was used for all determinations of blood pressure. Generally the cuff was placed on the upper part of the right arm of the subject and the calibrated mercury scale stood as high above the floor as the mattress of a bed.

The variations in blood pressure and pulse rate were observed (1) with the subject horizontal, after he had been lying quietly for a half hour, and (2) following his voluntary change to the upright position. This period of rest was particularly necessary if the blood pressure of the patients who had hypertension was to reach a basal level. Observations of blood pressure were made until two consecutive readings of the systolic pressure were within 2 mm. of each other and two consecutive readings of the diastolic pressure were likewise within 2 mm. of each other. The pulse rate was noted simultaneously with the reading of blood pressure. The voluntary change from the horizontal position to the upright one was made with the least possible muscular effort. Observations of blood pressure and pulse rate were noted one and two minutes after the change. The readings made after two minutes were recorded. Since patients with hypertension are most sensitive to psychic stimulation, the upright position was attained by voluntary movement of the patient rather than by means of the tilt table; motion of the tilt table tends to startle patients. Whenever a change in posture is mentioned in this paper, the change is always from the horizontal to the upright position.

The severity of the hypertension was graded by Dr. Wagener,<sup>13</sup> according to the appearance of the retinal arterioles and the presence or absence of retinitis. His classification is as follows: Group I, minimal amount of narrowing or sclerosis; Group II, moderate amount of sclerosis without active spasm; Group III, retinitis with moderate spasm and sclerosis, and Group IV, retinitis with spasm, sclerosis, and choked disks.

Resection of the splanchnic nerves, for lowering the blood pressure of patients with hypertension, was first suggested by Daniélopou<sup>6</sup> in 1923. In 1924 Pender<sup>7</sup> proposed, before the Congress of Internal Medicine at Milan, surgical treatment of arterial hypertension which consisted of resecting the left splanchnic nerves. Adson,<sup>11</sup> in 1925, performed bilateral lumbar sympathetic ganglionectomy and trunk resection in an attempt to lower the blood pressure. The operation included the second, third, and fourth lumbar ganglions on both sides, but definite drop in blood pressure did not occur. Neither did unilateral cervicothoracic sympathetic ganglionectomy produce an effect on the blood pressure of a patient who had hypertension. Following this, several foreign surgeons<sup>8, 9</sup> performed unilateral splanchnic resection on patients with hypertension and other arterial diseases, with some favorable results.

In 1930, Adson,<sup>3</sup> with the aid of Craig, sectioned the ventral roots of both sides from the sixth thoracic to the second lumbar inclusive. This operation is known as extensive bilateral, ventral rhizotomy. The systolic blood pressure dropped from 200 mm. to 100 mm. of mercury; unfortunately, postoperative hemorrhage developed, and although the clot was removed, partial spastic paraplegia developed and persisted. At this time this procedure was discontinued as an unsatisfactory one.

Craig,<sup>5</sup> in 1932, performed posterior, infradiaphragmatic resection of the splanchnic nerves with removal of the first lumbar ganglion. The operation was applied first to one side and then a similar technic was employed ten days to two weeks later on the other side. For convenience, this operation is designated as posterior, infradiaphragmatic, bilateral resection of the splanchnic nerves and bilateral removal of the first lumbar ganglions.

Since the patient on whom extensive rhizotomy had been performed still maintained a decrease in systolic and diastolic pressure after three years, with results far more striking than those produced by bilateral posterior, infradiaphragmatic resection of the splanchnic nerves and removal of the first lumbar ganglions, Adson<sup>2</sup> returned to extensive, bilateral, ventral rhizotomy in 1933. Whereas, in some of the cases the extensive, bilateral, ventral rhizotomy extended from the fifth thoracic to the second lumbar segments, inclusive, a modified operation was used in other cases so that in some instances the bilateral, ventral rhizotomy included the eleventh thoracic to the second lumbar inclusive, the tenth thoracic to the second lumbar inclusive, the ninth thoracic to the second lumbar inclusive, the eighth thoracic to the second lumbar inclusive, the seventh thoracic to the second lumbar inclusive, and the sixth thoracic to the second lumbar inclusive. In two instances, the ventral nerve roots from the sixth thoracic to the twelfth thoracic, inclusive, were sectioned. In two other instances, the extensive, ventral rhizotomy was performed in two stages, first from the tenth thoracic to the second lumbar, inclusive, and later from the sixth to the ninth thoracic, inclusive.

As the extensive rhizotomy, whether done in one or in two stages, was a formidable procedure, Adson,<sup>3</sup> in 1935, performed extensive resection of splanchnic nerves with partial removal of the celiac ganglion, removal of the first and second lumbar sympathetic ganglions and intervening trunks, and partial resection of the suprarenal gland. This operation was done in two stages, first on one side and, about two weeks later, on the other side.

Following the surgical procedures, readings of blood pressure and of pulse rate were not made until sufficient time had passed to eliminate all aspects of shock and general weakness. The period chosen was twenty-five to twenty-eight days after rhizotomy and the same length of time after the second operation of the two-stage procedure.

The methods used for determining the approach to completeness of the sympathetic denervation were a sweating test<sup>10</sup> performed by the cobaltous chloride and heat method and determination of the cutaneous increase in temperature<sup>12</sup> of the lower extremities. The cutaneous temperature was measured by means of the thermocouple described by Sheard.

#### MATERIAL

The readings of blood pressure and of pulse rate were determined on 183 subjects before and following voluntary change from the horizontal to the upright position. The subjects were divided into two major groups, depending on whether surgical procedures had or had not been performed.

Group I, or the group composed of subjects who were not operated on, included ninety individuals, and these were divided into two classes, description of which will appear in the respective paragraphs under "Results."

Group II, or the group composed of patients who were operated on, included ninety-three individuals, and these were divided into eight classes, description of which also will appear in the respective paragraphs under "Results."

## RESULTS

*Group I. Subjects Not Subjected to Operation*

*Class 1. Normal Subjects.*—The individuals of this class consisted of eighty physicians, nurses and other persons; all were in good health as far as could be determined. Their ages ranged from twenty to sixty years, inclusive, with an average age of thirty-four years. Assumption of the upright posture by these persons produced an average increase of 8 mm. in diastolic blood pressure and no increase in the systolic pressure. The cardiac rate increased an average of fourteen beats per minute (Table I).

TABLE I

AVERAGE VALUES OF BLOOD PRESSURE AND PULSE RATE FOR NORMAL INDIVIDUALS

	CASE	AGE (YEARS)	LYING			STANDING		
			BLOOD PRESSURE (MM. HG)		PULSE (BEATS PER MINUTE)	BLOOD PRESSURE (MM. HG)		PULSE (BEATS PER MINUTE)
			SYSTOLIC	DIASTOLIC		SYSTOLIC	DIASTOLIC	
Females	43	30.3	113.8	73.4	77.0	114.9	81.1	90.0
Males	37	37.6	114.5	71.2	75.3	112.6	80.7	91.1
Postural change, females			+1.1	+7.7	+13.0			
Postural change, males			-1.9	+9.5	+15.8			
Age 20 to 30 yr.	35		117.4	71.4	74.1	116.2	82.1	90.1
Age 30 to 40 yr.	24		112.2	72.8	77.0	115.3	82.8	87.7
Age 40 to 50 yr.	13		112.2	73.2	76.9	111.5	76.5	93.8
Age 50 to 60 yr.	8		109.0	74.3	82.2	102.8	77.1	95.3

TABLE II

BLOOD PRESSURE AND PULSE RATE WITH POSTURAL CHANGE IN CASES OF POSTURAL HYPOTENSION

	CASE	AGE (YEARS) AND SEX	LYING			STANDING		
			BLOOD PRESSURE (MM. HG)		PULSE (BEATS PER MINUTE)	BLOOD PRESSURE (MM. HG)		PULSE (BEATS PER MINUTE)
			SYSTOLIC	DIASTOLIC		SYSTOLIC	DIASTOLIC	
	1	44 M	120	92	84	60	44	88
	2	44 M	128	98	76	40		76
	3	64 M	138	90	80	64		88
	4	56 M	130	70	68	40		64
	5	45 M	135	95	75	50		
	6	55 M	130	80	84	85	50	96
	7	55 F	120	70	65	42		100
	8	35 M	128	78	60	88		Syncope
	9	41 F	168	108	84	60	54	100
	10	41 M	100	75	68	45	35	108
Average		48	129.7	85.6	74.7	57.4	45.7	90
Postural change			-72.3	-39.3	+15.3			

*Class 2. Patients Who Had Postural Hypotension.*—In this class were ten persons, whose ages ranged from thirty-five to sixty-four years inclusive, with an average age of forty-eight years. They are included in the report because abnormal findings associated with function of the vasomotor system were similar to those produced by certain operations on the sympathetic nervous system. The effects on blood pressure and pulse rate of rising from a lying to an upright posture are given in Table II.

*Group II. Patients Subjected to Operation*

*Class 1. Patients Subjected to Various Surgical Procedures Other Than on the Sympathetic Nervous System.*—The individuals of this class consisted of thirty-five patients. Their ages ranged from sixteen to

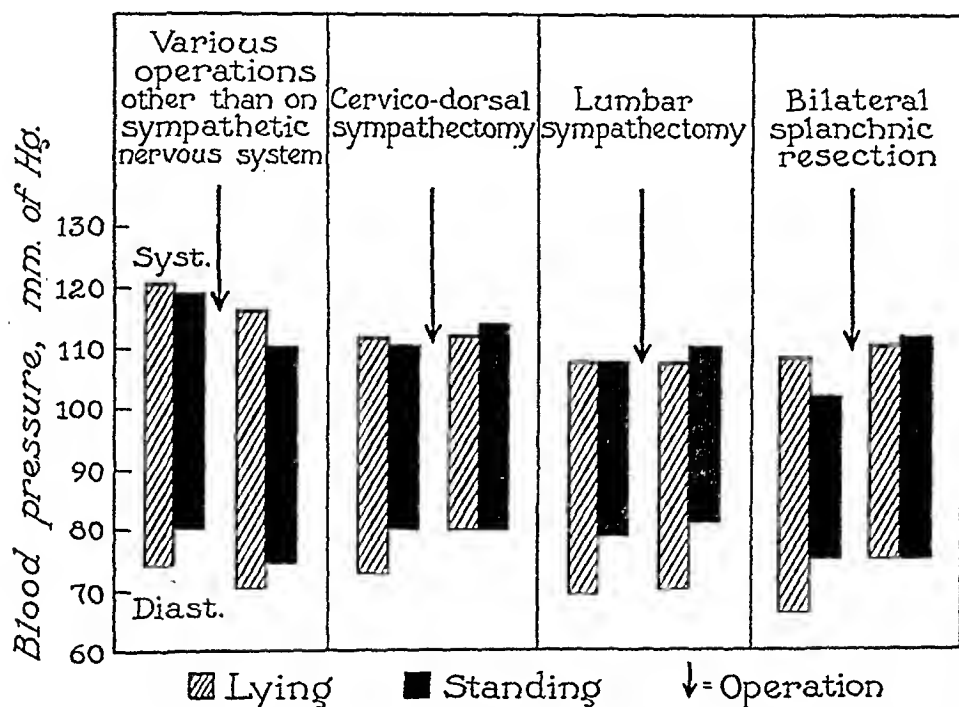


Fig. 1.—The effects of posture and operation on blood pressure. Before operation, the blood pressure of the patients represented was normal. From left to right the columns represent Classes 1, 2, 3 and 5.

seventy years, with an average age of forty-two years. The average blood pressure was 120 mm. of mercury systolic and 75 mm. diastolic. The patients were subjected to cholecystectomy, appendectomy, nephrectomy and laminectomy. The studies were made on this class to determine the effect of operation, if any, on the blood pressure and pulse rate, and the effect on the postural changes in blood pressure. Results are given in Tables III and IV and in Fig. 1.

*Class 2. Patients Subjected to Bilateral Cervicothoracic Sympathectomy (Adson-Craig Technique<sup>1</sup>).*—In this class were five patients, four of whom had Raynaud's disease and one of whom had essential hyperhidrosis. Their ages ranged from eighteen to thirty-five years, with an average age of twenty-eight years. Their blood pressure was within normal range. Results appear in Tables III and IV and Fig. 1.

TABLE III

THE AVERAGE INCREASE (+) OR DECREASE (-) IN BLOOD PRESSURE AND PULSE RATE AFTER VOLUNTARY CHANGE FROM THE HORIZONTAL TO THE UPRIGHT POSITION

CLASS	SUBCLASS	SUBJECTS	OPERATION	BEFORE OPERATION			AFTER OPERATION		
				CHANGE IN BLOOD PRESSURE (MM. HG)		CHANGE IN PULSE RATE (BEATS PER MIN.)	CHANGE IN BLOOD PRESSURE (MM. HG)		CHANGE IN PULSE RATE (BEATS PER MIN.)
				SYSTOLIC	DIASTOLIC		SYSTOLIC	DIASTOLIC	
1		35	Various major surgical procedures other than on the sympathetic nervous system	- 1.9	+ 5.7	+22.1	- 5.9	+ 2.2	+20.8
2		5	Bilateral cervicothoracic sympathectomy	+ 0.8	+ 6.6	+13.6	+ 0.8	+10.8	+11.0
3		6	Bilateral lumbar sympathectomy	0.0	+ 8.6	+18.7	+ 2.0	+11.7	+24.3
4		1	Bilateral section of intercostal nerves—7th to 11th inclusive	+20.0	0.0	+ 4.0	-20.0	0.0	+ 6.0
5		2	Bilateral section of splanchnic nerves with bilateral removal of the 1st and 2nd lumbar ganglions	- 5.0	+ 2.5	+20.0	+ 2.5	0.0	+47.0
6		6	Posterior infradiaphragmatic bilateral resection of splanchnic nerves and bilateral removal of the 1st lumbar ganglions	-9.0	+ 8.4	+11.8	- 9.1	+ 3.2	+12.3
7	1	1	Bilateral ventral rhizotomy, 11th thoracic—2nd lumbar, inclusive	0.0	+10.0	+22.0	-15.0	- 5.0	0.0
	2	6	Bilateral ventral rhizotomy, 10th thoracic—2nd lumbar, inclusive	- 9.8	+ 3.0	+17.1	-24.0	- 1.6	+16.0
	3	5	Bilateral ventral rhizotomy, 9th thoracic—2nd lumbar, inclusive	-19.0	+ 1.0	+13.6	-19.4	- 5.0	+19.2
	4	1	Bilateral ventral rhizotomy, 8th thoracic—2nd lumbar, inclusive	-34.0	+10.0	+12.0	-40.0	-15.0	+ 8.0
	5	1	Bilateral ventral rhizotomy, 7th thoracic—2nd lumbar, inclusive	+20.0	+10.0	+28.0	-70.0	-40.0	+40.0
	6	2	Bilateral ventral rhizotomy, 6th thoracic—12th thoracic	-16.0	+12.5	+14.0	-12.5	0.0	+24.5
	7	7	Bilateral ventral rhizotomy, 6th thoracic—2nd lumbar, inclusive	-21.4	- 3.9	+18.9	-49.8	-21.9	+29.6
	8	3	Bilateral ventral rhizotomy, 5th thoracic—2nd lumbar, inclusive	-11.0	+ 1.6	+10.0	-28.3	-16.0	+14.7
8		12	Bilateral splanchnic resection, partial resection of the coeliac plexus and bilateral partial resection of the suprarenal glands, with bilateral removal of the first and second lumbar ganglions and the intervening trunks	- 0.5	+ 5.3	+12.0	-21.4	-10.5	+32.9

TABLE IV

THE AVERAGE INCREASE (+) OR DECREASE (-) IN BLOOD PRESSURE  
AND PULSE RATE AS A RESULT OF OPERATION\*

CLASS	SUBCLASS	SUBJECTS	OPERATION	HORIZONTAL POSITION CHANGE IN BLOOD PRESSURE (MM. HG)		CHANGE IN PULSE RATE (BEATS PER MINUTE)	UPRIGHT POSITION CHANGE IN BLOOD PRESSURE (MM. HG)		CHANGE IN PULSE RATE (BEATS PER MINUTE)
				SYSTOLIC	DIASTOLIC		SYSTOLIC	DIASTOLIC	
1		35	Various major surgical procedures other than on the sympathetic nervous system	- 4.5	- 2.9	+ 2.1	- 8.5	- 6.4	+ 1.8
2		5	Bilateral cervicothoracic sympathectomy	+ 0.8	+ 1.2	+ 8.0	+ 0.8	+ 6.4	+ 5.4
3		6	Bilateral lumbar sympathectomy	0.0	+ 1.6	- 1.3	+ 1.8	+ 4.7	+ 4.3
4		1	Bilateral section of intercostal nerves—7th to 11th, inclusive	+30.0	+10.0	+ 6.0	-10.0	+10.0	+ 8.0
5		2	Bilateral section of splanchnic nerves with bilateral removal of 1st and 2nd lumbar ganglions	+ 3.5	+ 2.5	+17.0	+10.0	0.0	+44.0
6		6	Posterior infradiaphragmatic bilateral resection of splanchnic nerves and bilateral removal of the first lumbar ganglions	-14.0	- 3.8	+ 4.5	-14.1	- 8.9	+ 5.0
7	1	1	Bilateral ventral rhizotomy, 11th thoracic—2nd lumbar, inclusive	- 5.0	+10.0	+ 8.0	-20.0	- 5.0	-14.0
	2	6	Bilateral ventral rhizotomy, 10th thoracic—2nd lumbar, inclusive	-19.0	- 5.5	+ 5.1	-32.3	-10.1	+ 4.0
	3	5	Bilateral ventral rhizotomy, 9th thoracic—2nd lumbar, inclusive	-30.0	-17.0	+ 6.4	-30.4	-23.0	+12.0
	4	1	Bilateral ventral rhizotomy, 8th thoracic—2nd lumbar, inclusive	-34.0	-20.0	- 6.0	-40.0	-45.0	-10.0
	5	1	Bilateral ventral rhizotomy, 7th thoracic—2nd lumbar, inclusive	-10.0	-20.0	-12.0	-100.0	-70.0	0.0
	6	2	Bilateral ventral rhizotomy, 6th thoracic—12th thoracic, inclusive	-40.0	-12.5	-15.5	-36.5	-25.0	- 5.0
	7	7	Bilateral ventral rhizotomy, 6th thoracic—2nd lumbar, inclusive	-44.3	-27.2	+ 4.6	-72.6	-45.2	+15.3
	8	3	Bilateral ventral rhizotomy, 5th thoracic—2nd lumbar, inclusive	-61.0	-38.4	+ 9.3	-78.3	-56.6	+14.0
8		12	Bilateral splanchnic resection, partial resection of the celiac plexus and bilateral partial resection of the suprarenal glands, with bilateral removal of the first and second lumbar ganglions and the intervening trunks	-42.7	-18.5	+ 1.1	-63.6	-34.3	+21.8

\*The purpose of this table is not to be confused with that of Table III. Whereas the primary purpose of Table III is to show the effect of change in posture, the primary purpose of Table IV is to show the effect of operation.

*Class 3. Patients Subjected to Bilateral Lumbar Sympathectomy (Adson-Craig Technique<sup>1</sup>).*—In this class were six patients, one of whom had Raynaud's disease, four of whom had chronic infectious arthritis and one of whom had thromboangiitis obliterans. Their ages ranged from fourteen to forty-three years with an average age of thirty-two years. The blood pressure readings were within normal range. Results appear in Tables III and IV and Fig. 1.

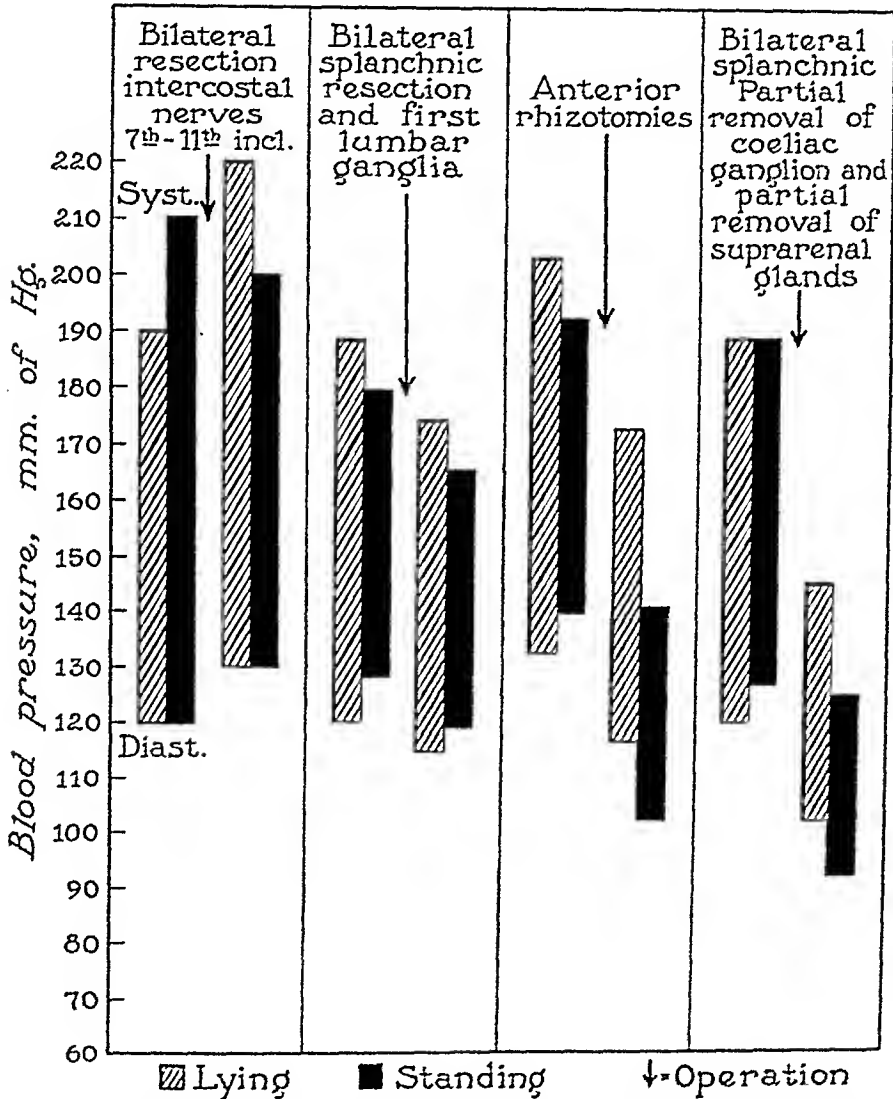


Fig. 2.—The effects of posture and operation on blood pressure. The patients had essential hypertension. From left to right the columns represent Classes 4, 6, 7 and 8.

*Class 4. A Patient Subjected to Bilateral Section of Intercostal Nerves From the Seventh to the Eleventh, Inclusive.*—This class is represented by only one patient. He was fifty-three years of age and had essential hypertension of a severity which would place his case in Wagener's Group III. This operation was performed because some of the patients with postural hypotension and some of the patients follow-

ing ventral rhizotomy had experienced, when in the upright position, an elevation of blood pressure above the level of syncope, after application of a tight abdominal binder. Therefore, the suggestion was made that relaxation of the intercostal and abdominal muscles would decrease the blood pressure, particularly when the subject was in the upright position. Results are given in Tables III and IV and Fig. 2.

*Class 5. Patients Subjected to Bilateral Section of Splanchnic Nerves, With Bilateral Removal of the First and Second Lumbar Ganglions.*—This class is represented by two patients, one aged twenty-two years and the other forty-one years, whose blood pressure was normal. Operation was performed for postcholecystectomy pain in one case and for megacolon in the other. Results are given in Tables III and IV and Fig. 1.

*Class 6. Patients Subjected to Posterior Infradiaphragmatic Bilateral Resection of Splanchnic Nerves and Bilateral Removal of the First Lumbar Ganglions.*—This class is represented by six patients who had essential hypertension. Their ages ranged from twenty-two to forty-six years, with an average age of thirty-seven years. The average systolic blood pressure in the horizontal position before operation was 188.1 mm. The average diastolic blood pressure in the horizontal position before operation was 119.1 mm. Other data are given in Tables III and IV and Fig. 2.

*Class 7. Bilateral Ventral Rhizotomy.*—This class is represented by twenty-six patients, all of whom had essential hypertension of varying severity. The class is divided into eight subclasses, depending on the extent of the rhizotomy.

*Subclass 1. Bilateral ventral rhizotomy from the eleventh thoracic to the second lumbar, inclusive.* The operation at this level was performed on one woman, aged twenty-eight years, who had essential hypertension, which by Wagener's classification would be of Group II. The systolic blood pressure in the horizontal position before operation was 185 mm. of mercury and the diastolic blood pressure under the same conditions was 120 mm. The pulse rate, before operation, increased from 88 beats per minute in the horizontal position to 110 beats in the upright position. Other data are given in Tables III and IV and in Figs. 2 and 3.

*Subclass 2. Bilateral ventral rhizotomy from the tenth thoracic to the second lumbar, inclusive.* Six patients were operated on at this level. The ages ranged from thirty-seven to fifty-one years, with an average age of forty-four years.

All the patients except one had very severe essential hypertension, Group III or IV (Wagener's classification). The hypertension of the exceptional patient was of Group II. Before operation, with the patient in the horizontal position, the average systolic blood pressure was 194.6 mm. Following operation, when the patient was in the horizontal posi-



tion, the average systolic blood pressure was 175.6 mm. The postural change in this group was more than twice as great following operation as before operation. The average diastolic blood pressure before operation was 121.3 mm. Other results are given in Tables III and IV and in Figs. 2 and 3.

Subclass 3. Bilateral ventral rhizotomy from the ninth thoracic to the second lumbar, inclusive. Five patients were operated on. The ages ranged from forty-four to fifty-three years, with an average age of fifty years. They all had essential hypertension (Wagener's Group III). The average systolic blood pressure in the horizontal position before operation was 215 mm. This decreased to 196 mm. when the up-

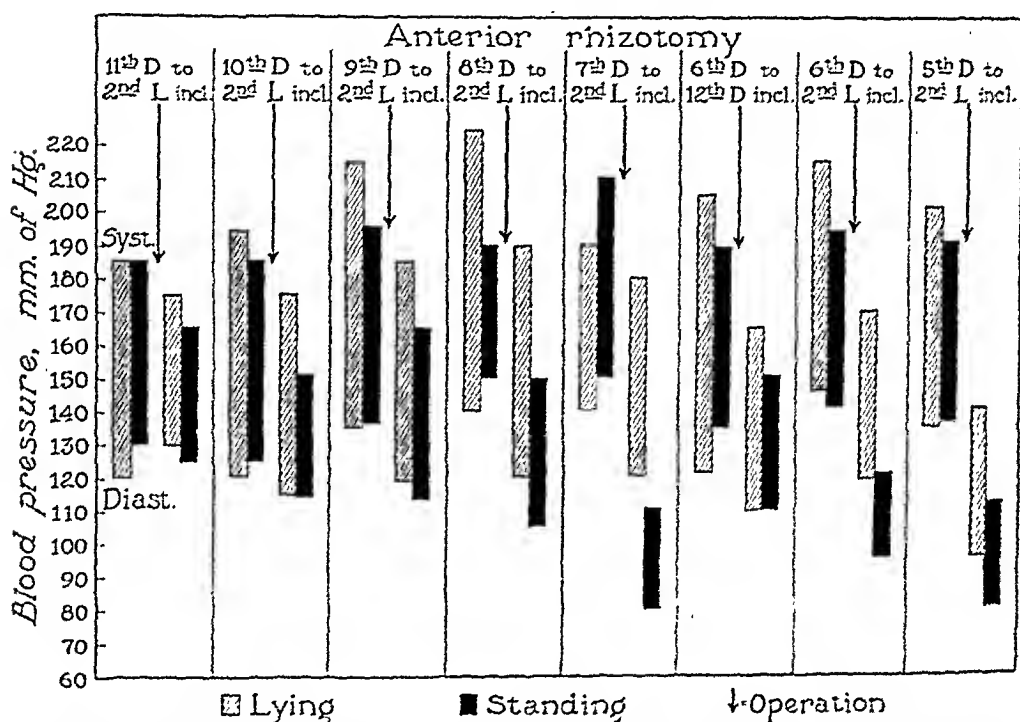


Fig. 3.—The effects of posture and operation on blood pressure. The patients had essential hypertension. The columns represent, in order from left to right, the eight subclasses of Class 7.

right position was assumed. In this group the postural change of the systolic blood pressure before and after operation was the same, even though the actual pressure in both positions was 30 mm. less after operation than before operation. Before operation the average diastolic blood pressure was 136 mm. when the patient was in the horizontal position and remained the same when he assumed the upright position. The average pulse rate before operation, in the horizontal position, was 76.8 beats per minute. Other data are give in Tables III and IV and in Figs. 2 and 3.

Subclass 4. Bilateral ventral rhizotomy from the eighth thoracic to the second lumbar, inclusive. One patient, aged thirty-six years, who

had essential hypertension of Wagener's Group II, underwent rhizotomy at this level. Before operation, with the patient in the horizontal position, the systolic blood pressure was 224 mm. The changes of the systolic pressure resulting from posture were definitely decreased both before and after operation. The diastolic blood pressure in the horizontal position, before operation, was 140 mm. The pulse rate in the horizontal position before operation was 88 beats per minute. Other results are given in Tables III and IV and in Figs. 2 and 3.

Subclass 5. Bilateral ventral rhizotomy from the seventh thoracic to the second lumbar, inclusive. One patient, aged thirty years, who had essential hypertension, Group IV (Wagener's classification), was subjected to this operation. The systolic blood pressure before operation, in the horizontal position, was 190 mm. Following operation, in the change from the horizontal to the upright posture, the systolic blood pressure changed markedly in comparison with the postural change before operation. The diastolic blood pressure in the horizontal position before operation was 140 mm. After operation, in the change from the horizontal to the upright posture, the diastolic pressure decreased to a level of 80 mm. of mercury. This was 50 mm. less than the postural change before operation. The pulse rate before operation in the horizontal position was 92 beats per minute. Other results are given in Tables III and IV and in Figs. 2 and 3.

Subclass 6. Bilateral ventral rhizotomy from the sixth thoracic to the twelfth thoracic, inclusive. Two patients underwent this operation. Their ages were thirty-five and thirty-eight years, respectively. Both had essential hypertension of Wagener's Group IV. The average systolic blood pressure in the horizontal position before operation was 205 mm. of mercury. After operation, the change in blood pressure produced by assumption of the upright position was not as great as before operation although the pressures were definitely lower: 165 mm. in the horizontal position and 153.5 mm. in the upright position. The average diastolic blood pressure in the horizontal position before operation was 122.5 mm. The average pulse rate in the horizontal position before operation was 92 beats per minute. Other results are given in Tables III and IV and in Figs. 2 and 3.

Subclass 7. Bilateral ventral rhizotomy from the sixth thoracic to the second lumbar, inclusive. Seven patients were subjected to this operation. Their ages ranged from twenty-three to forty-five years, with an average age of thirty-four years. All had essential hypertension. Of five, the condition was of Group III (Wagener's classification); of one, Group III plus, and of one, Group IV. The average systolic blood pressure in the horizontal position before operation was 215.7 mm. The decrease in systolic blood pressure caused by voluntary change in posture (horizontal to upright; measurements made after operation only) was

slightly greater than the decrease in systolic blood pressure caused by operation (measurements made in the horizontal position only). The change in blood pressure caused by change of posture (mentioned in the previous sentence) was not nearly so great as the difference between the blood pressure before and after operation (measurements made in the upright position only). The average diastolic blood pressure in the horizontal position before operation was 145.7 mm. of mercury. There was a definite decrease in the diastolic pressure caused by voluntary change in posture (horizontal to upright, measurements made after operation only). The decrease mentioned in the preceding sentence was only half as great as the difference between the diastolic blood pressure before and after operation (measurements made in the upright position only). After operation there was a definite decrease in the diastolic blood pressure but only one-half as great as the difference in the diastolic pressure in the upright position following operation. The average pulse rate in the horizontal position before operation was 87.4 beats per minute. Other results are given in Tables III and IV and in Figs. 2 and 3.

Subclass 8. Bilateral ventral rhizotomy from the fifth thoracic to the second lumbar. Three patients were subjected to this operation. Their ages ranged from twenty-two years to forty-two years, with an average age of thirty-two years. The first patient had essential hypertension, Group II (Wagener's classification) and the other two had essential hypertension, Group III. The average systolic pressure in the horizontal position before operation was 202.6 mm. of mercury. The change in systolic blood pressure caused by operation (measurements made in the same position after, as before, operation) was nearly three times as great as the change in systolic blood pressure caused by voluntary change in posture (horizontal to upright, measurements made after operation only). The average diastolic pressure in the horizontal position before operation was 135 mm. of mercury. The decrease in diastolic blood pressure with voluntary change in posture (horizontal to upright, measurements made after operation only) was not nearly so great as that caused by operation (measurements made in the same position after, as before, operation). The average pulse rate in the horizontal position before operation was 78 beats per minute. Other figures are given in Tables III and IV and Figs. 2 and 3.

*Class 8. Patients Subjected to Bilateral Splanchnic Resection, Partial Resection of the Celiac Plexus and Bilateral Partial Resection of the Suprarenal Glands, With Bilateral Removal of the First and the Second Lumbar Ganglions and the Intervening Trunks.*—This class was represented by twelve patients who had essential hypertension of varying severity. Their ages ranged from twenty-one to forty-seven years, with

an average age of thirty-three years. Four of them had essential hypertension, of Group II (Wagener's classification), and eight had essential hypertension, Group III. The average systolic blood pressure was 188.5 mm. The change from the horizontal to the upright position following operation produced marked change in the systolic blood pressure in comparison to the decrease with change of posture before operation. The postural change mentioned in the preceding sentence was only one-half as great as the change caused by operation (measurements made in the horizontal position only) and one-third as great as the change caused by operation (measurements made in the upright position only). The average diastolic blood pressure in the horizontal position before operation was 120.9 mm. In the change from the horizontal to the upright position (measurements made after operation only) the decrease in diastolic blood pressure was only one-third as great as the difference between the diastolic pressure before and after operation (measurements made in the upright position only). The average pulse rate before operation was 83.8 beats per minute. Other results are given in Tables III and IV and in Figs. 2 and 3.

#### COMMENT

The problem of the maintenance of blood pressure is more complicated in man than in animals because of the added factor of gravity consequent to the upright position of man. This implies in man either a mechanism which is more complex or which maintains a more delicate regulatory control over the mass of blood in the body. When a man rises from the horizontal to the upright position, the blood tends to accumulate in parts below the level of the heart and the supply to the brain tends to diminish. Theoretically, this diminution stimulates the vasomotor center which sends out impulses constricting the arterioles generally. The vasoconstrictor action in the splanchnic region is probably most significant and in normal man prevents a fall in blood pressure. If this constriction of the arterioles of the splanchnic region in man is the dominant mechanism in the maintenance of blood pressure in the upright position, interruption of the passage of impulses from the vasomotor center to the splanchnic arterioles should remove some of this control and allow a definite drop in the blood pressure, particularly in the upright position. It should be possible to remove this control by section of the splanchnic nerves.

The splanchnic nerves of animals have been sectioned, but the investigations reported were not comparable to this study because the observations on blood pressure were made under anesthesia in some instances and in all cases in one position, the horizontal one. In the present study the observations of blood pressure and pulse rate were made on human subjects in both the horizontal and the upright positions.

Sufficient time was allowed for the subjects to recover from surgical shock so that the experiments were not acute and were not complicated by anesthesia.

It is interesting to note that in observations of human subjects whose blood pressure was normal, the blood pressure was found to be practically unchanged by various operations, including extensive splanchnic resection. Even in the upright position their blood pressure was the same after operation as before it.

The patients who had essential hypertension and who underwent bilateral, posterior, infradiaphragmatic resection of the splanchnic nerves showed practically the same change in blood pressure when they assumed the upright position following operation as they had shown before operation. Since the splanchnic nerves may show a varied anatomical distribution, the denervation may not have been complete in this operation.

In the cases in which partial ventral rhizotomy was performed, it is evident that unless complete denervation of the splanchnic region was accomplished, no great change in blood pressure took place in the shift from the horizontal to the upright position. After extensive ventral rhizotomy, at least from the seventh thoracic to the second lumbar, inclusive, the effect of posture in decreasing the blood pressure was practically twice as great as before operation. With this operation, section of fibers which formed the splanchnic nerves, along with denervation of the suprarenal glands and paralysis of the muscles of the abdominal wall, were effected. The question might be raised as to the influence of the loss of muscular tone of the abdominal wall. In one case bilateral section of the intercostal nerves from the seventh to the eleventh inclusive was done and caused paralysis of the muscles of the abdominal wall but caused no effect on the blood pressure when the upright position was assumed from the horizontal. This would appear to demonstrate that relaxation of the intercostal and abdominal muscles alone was not sufficient to lower the blood pressure in this instance and that the vasomotor system plays the predominant rôle in the decrease of blood pressure when the upright position is assumed from the horizontal position. Whereas relaxation of the intercostal and abdominal muscles obviously was not a dominant factor in the lowering of the blood pressure in this particular case, it is probably an accessory but minor factor in lowering the blood pressure following extensive rhizotomy. Evidence of this has been obtained by application of a tight abdominal binder which prevented the marked fall in blood pressure as a result of the upright position. Denervation or resection of the suprarenal glands alone apparently has not greatly affected the blood pressure in cases of essential hypertension. In one case of essential hypertension, not referred to.

here, but mentioned by Adson, Craig, and Brown in their paper, Walters completely removed one suprarenal gland and removed three-fifths of the other suprarenal gland but produced little effect on the blood pressure.

In the last group of patients on whom bilateral splanchnic resection, partial resection of the celiac plexus and bilateral partial resection of the suprarenal glands with bilateral removal of the first and second lumbar ganglions and the intervening trunks were performed, the results of posture on blood pressure were practically the same as in the cases of extensive ventral rhizotomy. Whereas resection of the lumbar ganglions alone did not cause the blood pressure in the upright position to be less after operation than it had been in the same position before operation, when performed in addition to bilateral resection of the splanchnic nerves, it seemed to furnish by vasodilatation a larger vascular bed with less resistance, thereby helping to lower the blood pressure. Evidence of the importance of lumbar ganglionectomy was given by the effect on the blood pressure of two patients who were subjected to bilateral ventral rhizotomy from the sixth to the twelfth thoracic, inclusive, and by the effect on the blood pressure of the group of patients who underwent ventral rhizotomy from the sixth thoracic to the second lumbar, inclusive. The decrease in blood pressure, with change from the horizontal to the upright position, was three times as great following the latter as following the former operation.

In this study, the similarity between postural hypotension and the results obtained by anterior rhizotomy is evident. Following extensive ventral rhizotomy, the postural effects produced and the loss of sweating were the same as in some cases of postural hypotension.

Operation on the sympathetic nervous system does not cause much change in blood pressure of normal individuals but does cause change in blood pressure of persons who have essential hypertension. The question arises as to the cause of this difference. The etiology of essential hypertension is not definitely known. It has been suggested that it may be either a central abnormality, such as hypersensitivity of the vasomotor center in the diencephalon, or an abnormality of the peripheral mechanism. It is possible that normal blood pressure is maintained automatically without much participation of a central pressor mechanism, whereas increased blood pressure results somewhat from a central pressor mechanism, disconnection of which from the peripheral effectors allows a drop in blood pressure when the patient stands.

It is evident from these studies that significant decreases in blood pressure of patients who have essential hypertension, particularly in the upright position, are not produced by surgical methods except when extensive abdominal sympathetic denervation is effected.

## SUMMARY

Before posterior infradiaphragmatic bilateral resection of the splanchnic nerves and bilateral removal of the first lumbar ganglions, voluntary change to the upright from the horizontal position in six patients who had essential hypertension caused an average decrease of 9 mm. in the systolic blood pressure and an average increase of 8.4 mm in the diastolic blood pressure. The cardiac rate increased an average of 11.8 beats per minute. Following operation, assumption of the upright position produced an average decrease of 9.1 mm. in the systolic blood pressure and an average increase of 3.2 mm. in the diastolic blood pressure. The cardiac rate increased an average of 12.3 beats per minute.

Voluntary change from the horizontal to the upright position by twenty-six patients, after ventral rhizotomy, caused varied results according to the extensiveness of denervation. Before operation, assumption of the upright position by one patient caused no change in the systolic blood pressure and an increase of 10 mm. of mercury in the diastolic blood pressure. The heart rate increased 22 beats per minute. This patient was subjected to ventral rhizotomy from the eleventh thoracic to the second lumbar, inclusive. Following operation, assumption of the upright position produced a decrease of 15 mm. in the systolic blood pressure and a decrease of 5 mm. in the diastolic blood pressure. The cardiac rate was unchanged. Before operation, assumption of the upright position by seven patients who had essential hypertension caused an average decrease of 21.4 mm. of mercury in the systolic blood pressure and an average decrease of 3.9 mm. in the diastolic blood pressure. The average cardiac rate was increased 18.9 beats per minute. These patients were subjected to ventral rhizotomy from the sixth thoracic to the second lumbar, inclusive. Following operation, assumption of the upright position produced an average decrease in the systolic blood pressure of 49.8 mm. and an average decrease of 21.9 mm. in the diastolic blood pressure. The heart rate increased an average of 29.6 beats per minute. Rhizotomy between these two levels gave results almost in proportion to the extensiveness of the sympathetic denervation.

Before extensive bilateral splanchnic resection, partial resection of the celiac plexus and bilateral partial resection of the suprarenal glands, with bilateral removal of the first and second lumbar ganglions and the intervening trunks, assumption of the upright position by twelve patients who had essential hypertension produced no change in the systolic blood pressure and an average increase in the diastolic blood pressure of 5.3 mm. The pulse rate increased an average of 12 beats per minute. Following operation, assumption of the upright position produced an average decrease of 21.4 mm. in the systolic blood pressure and an average decrease of 10.5 mm. in the diastolic blood pressure. The pulse rate increased an average of 32.9 beats per minute. In both the group of

cases in which extensive rhizotomy was performed, and in this group, the decrease of 21.4 mm. caused by posture was only about one-third as great as the total decrease caused by a combination of operation and posture. It would seem, therefore, that the lowered blood pressures following these surgical procedures are ascribable one-third to an introduced postural effect and two-thirds to the effects of the operations themselves.

Finally, significant decreases in blood pressure of patients who had essential hypertension, particularly when they were in the upright position, were not produced by surgical methods except when extensive abdominal sympathetic denervation was effected. When less radical operations were performed, the magnitude of the decrease seemed roughly proportional to the extent of the denervation.

#### REFERENCES

1. Adson, A. W., and Brown, G. E.: The Treatment of Raynaud's Disease by Resection of the Upper Thoracic and Lumbar Sympathetic Ganglia and Trunks, *Surg., Gynec. & Obst.* 48: 577, 1929.
2. Adson, A. W., and Brown, G. E.: Malignant Hypertension. Report of a Case Treated by Bilateral Section of Anterior Spinal Nerve Roots From the Sixth Thoracic to the Second Lumbar, Inclusive, *J. A. M. A.* 102: 1115, 1934.
3. Adson, A. W., Craig, W. McK., and Brown, G. E.: Surgery in Its Relation to Hypertension, *Surg., Gynec. & Obst.* 62: 314, 1936.
4. Brown, G. E., and Craig, W. McK.: The Physiological Effects of Unilateral and Bilateral Resection of the Major and Minor Splanchnic Nerves in Man, *Tr. A. Am. Physicians* 48: 213, 1933.
5. Craig, W. McK., and Brown, G. E.: Unilateral and Bilateral Resection of the Major and Minor Splanchnic Nerves: Its Effects in Cases of Essential Hypertension, *Arch. Int. Med.* 54: 577, 1934.
6. Daniélopou, D.: Quoted by Pereira.<sup>9</sup>
7. Pende, N.: Quoted by Santucci. Santucci, Gastone. *La thérapeutique chirurgicale de l'hypertension artérielle selon la méthode de Pende*, Clinique, Paris 27: 9, 1932.
8. Pieri, Gino: La resezione dei nervi splanchnici. Contributo tecnico alla chirurgia del sistema nervosa vegetativo, *Ann. ital. di chir.* 6: 678, 1927.
9. Pereira, António: *Nervi splanchnici*, Porto, Portugal, 1929, Tipografia, Porto Médico. Ltd., 331 pp.
10. Roth, Grace M.: A Clinical Test for Sweating, *Proc. Staff Meet. Mayo Clinic* 10: 383, 1935.
11. Rowntree, L. G., and Adson, A. W.: Bilateral Lumbar Sympathetic Neurectomy in the Treatment of Malignant Hypertension. Report of a Case, *J. A. M. A.* 85: 959, 1925.
12. Sheard, Charles: The Electromotive Thermometer: An Instrument and a Method for Measuring Intramural, Intravenous, Superficial and Cavity Temperatures, *Am. J. Clin. Path.* 1: 209, 1931.
13. Wagener, H. P.: The Clinical Interpretation of Retinal Vascular Lesions in Hypertension and Nephritis. (In press.)



## Department of Clinical Reports

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### ANGINA PECTORIS AT THE AGE OF FOURTEEN ASSOCIATED WITH CONGENITAL RUDIMENTARY RIGHT CORONARY ARTERY AND RUDIMENTARY POSTERIOR CUSP OF MITRAL VALVE

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CASE HISTORY.—J. F., a white schoolgirl, aged fourteen years, was admitted to the Wichita Falls Clinic-Hospital on Nov. 5, 1936, complaining of attacks of severe precordial pain.

She had had "rheumatism" at the age of six and was confined to bed for a period of two weeks at that time. The knees were stiff and swollen, but no elevation of temperature was recorded. Following this illness, she had noticed slight dyspnea when playing out of doors with other children. Otherwise, except for chickenpox, measles, and whooping cough, she had been well until the time of her present illness.

Present illness began in Dec., 1935. Following exposure to cold she suddenly complained late one afternoon of severe substernal pain radiating up into the neck and into the left arm. The pain ceased spontaneously. Similar attacks occurred every afternoon for the next week, after which they became more frequent and severe. The family physician was called and the patient was put to bed. After a month of rest in bed she began to get up and around the house though attacks continued. Mild attacks were relieved by merely standing erect; severe attacks required morphine.

During the extreme hot weather of the summer of 1936, she began to complain of dyspnea, which gradually became severe. The attacks of pain began to come at very frequent, though irregular, intervals. In the morning and late in the afternoon they would occur every twenty minutes unless morphine was given for relief. During the rest of the day and night they would occur at intervals of one or two hours. The attacks were always induced by excitement or by the slightest exertion.

On Nov. 5, 1936 she was brought to the hospital. Soon after admission she was seen in a typical attack. She suddenly complained of agonizing substernal pain which forced her to stand erect. The pain radiated up into the left side of neck and down the left arm. Just before the attack occurred her blood pressure was 140/0 mm. but during the attack it rose to 230/0 mm. Her heart rate increased from 100 to 130 and numerous extrasystoles appeared.

Physical examination showed an apprehensive, dyspneic, cyanotic girl, fairly well developed, and poorly nourished. There was marked pulsation of the vessels of the neck.

Examination of the heart showed the rate to be 100, with occasional extrasystoles. The apex impulse was heaving and forceful. There was marked enlargement, with the left border in the anterior axillary line in the sixth interspace. A systolic murmur of moderate intensity was heard all over the precordium. Along the left sternal border and at the apex there was a loud blowing diastolic murmur, immediately following the second sound.

The lungs were clear. The liver edge was barely palpable below the right costal margin. There was slight edema of the ankles. There was marked pulsation of all peripheral vessels. Her examination otherwise was negative. Her temperature was normal throughout entire period of hospitalization.

*Laboratory Findings.*—Urine: acid, specific gravity 1.020, albumin none, sugar none, sediment negative. Renal function tests normal. Blood: Wassermann test negative, hemoglobin 80 per cent, erythrocyte count on repeated examinations—3,950,000 to 4,500,000, leukocyte count on repeated examination 7,900 to 8,600.

X-ray examination of the heart showed the following:

Six-foot films of the chest showed no pulmonary abnormality, but a very large cardiac shadow which appeared to be a generalized hypertrophy without the diagnostic shape of any particular lesion was evident.

The electrocardiogram showed the following: P-waves normal. P-R interval .18 second. There was left axis deviation.  $T_1$  inverted.  $T_2$  and  $T_3$  upright. There were occasional ectopic beats of ventricular origin.

*Clinical Diagnosis.*—Valvular disease: chronic cardiac; aortic insufficiency; angina pectoris; hypertension.

*Treatment.*—Immediately following admission to the hospital, the patient was given 1 c.c. of salyrgan intravenously and was digitalized. Dyspnea was completely relieved in twenty-four hours, but typical attacks of angina pectoris continued. Nitroglycerin administered under the tongue gave relief in a very few minutes.

After a few days of rest in bed, the attacks became much less frequent, occurring only from four to eight times in twenty-four hours. Aminophyllin was then given for a period of two weeks without apparent benefit. On December 3 the patient began to sit up in a chair for twenty minutes twice a day. Following this her activity was gradually increased. Attacks of angina were no less frequent until Jan. 4, 1937, after which they occurred only once or twice in twenty-four hours. When free of pain her blood pressure was generally about 160/0 mm. During attacks it rose to between 200 and 220 systolic but the diastolic pressure remained at 0. The patient gained much strength. Her weight increased from 96 to 104 pounds. On February 5 she was discharged greatly improved.

On February 8 she returned complaining of severe abdominal pain of thirty-six hours' duration. Physical signs typical of acute appendicitis were present. Leucocyte count was 21,000. Under morphine, evipal, and novocaine anesthesia the abdomen was opened and a gangrenous appendix was removed. Immediate postoperative condition was excellent. The next day her temperature gradually rose to 108° F. Heart rate increased to 140. She became pale, weak, and delirious. All pain was controlled by morphine. Exitus occurred on the third day following operation. Permission to perform an autopsy was obtained, but examination was limited to the abdomen and heart, and it was requested that all the organs be returned to the body.

#### PATHOLOGICAL REPORT

The appendix removed Feb. 8, 1937, measured 6 cm. by 7 mm. It was acutely inflamed and covered with exudate. There was pus in the lumen. The walls were densely infiltrated with polymorphonuclear leucocytes and there were many small necrotic areas throughout.

*Autopsy Findings.*—There were no signs of generalized peritonitis. The appendiceal stump was apparently in good condition. It was surrounded by a localized peritonitis of moderate severity.

The pericardial sac contained about 40 c.c. of straw-colored fluid. The heart was moderately enlarged; weighing 425 grams. The bulk of the heart consisted of a greatly hypertrophied left ventricle, the walls of which measured 19 mm. in thickness. The right ventricle was atrophic, the walls measuring only 3 mm. in thickness. The

pulmonic and tricuspid valves were normal. The aortic ring was markedly dilated. The aortic cusps showed no vegetation and were normal except for a rolled appearance of the edges, due to the dilation of the aortic ring. The mitral valve consisted of a large anterior cusp only. The posterior cusp was practically absent. The left coronary artery appeared to be normal though large. The right coronary artery was rudimentary consisting of a small indentation into which no probe could be pushed. The course of the right coronary artery could not be followed over the surface of the ventricle. The conditions under which the autopsy was performed did not permit injection or dissection of the coronary arteries. There were no areas of infarction.

Microscopic examination of the wall of the right ventricle showed atrophy of the muscle fibers, fatty invasion about the arterioles and replacement fibrosis. Microscopic examination of the left ventricle showed hyperplasia and thickening of the muscle fibers. There was no pathological cellular infiltration of the muscle of either ventricle.

Microscopic examination of sections of the aortic and mitral valve cusps showed no pathology.

*Anatomical Diagnosis.*—1. Congenital abnormality of the heart: rudimentary posterior cusp of the mitral valve; rudimentary right coronary artery. 2. Appendicitis: acute with abscess. 3. Peritonitis: local.

#### COMMENT

Angina pectoris in early life is probably not as uncommon as a survey of the literature would indicate. No recent case reports can be found.

Attention is called to the clinical diagnosis of valvular disease, which was based upon the physical findings and the history of "rheumatism" followed by progressively increasing symptoms of heart failure.

Post mortem, no signs of inflammatory reaction could be found on the heart valves or in the heart muscle. A congenital insufficiency of the mitral valve increased the work of the left ventricle, apparently causing the hypertrophy of the muscle. No cause for the insufficiency of the aortic valve could be found other than the greatly dilated aortic ring resulting from the deformity of the heart.

The marked difference in the appearance and size of the ventricles of the heart was accounted for by the inadequate blood supply of the right ventricle and the increased work of the left ventricle.

The poor development of the right coronary artery was apparently congenital in origin although the possibility of a thrombosis with subsequent atrophy sometime after birth cannot be entirely excluded.

The relationship of the hypertension to the other findings is not clear except that it was another load to be carried by the burdened left ventricle.

The anatomical basis for angina pectoris in this case cannot be definitely established. It is probable that the following factors were of greatest importance: A blood supply to the right ventricle which had been inadequate since birth; a blood supply to the left ventricle, which though adequate at first, was rendered inadequate by hypertrophy and by increasing work.

# COARCTATION OF THE AORTA (ADULT TYPE); CONGENITAL BICUSPID AORTIC VALVE; SUBACUTE BACTERIAL ENDOCARDITIS

## CASE REPORT\*

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THE following case is reported for several reasons besides its comparative rarity. Our patient illustrated two common complications of this defect which are of clinical importance, namely, the association of coarctation of the aorta with congenital bicuspid aortic valve and the tendency for the malformed valve to become the seat of an infective endocarditis. In addition, a histological examination of serial sections through the subdividing ridge of the bicuspid valve was made to prove its congenital origin.

According to Abbott,<sup>1</sup> the incidence of bicuspid aortic valve in relation to a given number of consecutive autopsies has not been accurately determined but she believes it probably approximates that of Osler's,<sup>2</sup> and of Lewis and Grant's<sup>3</sup> series (1.3 and 1.4 per cent respectively). Coarctation of the aorta of the adult type is of much greater rarity, being found in only 0.006 per cent of a large series of necropsies gathered by Blackford.<sup>4</sup> The frequency with which both defects are associated has been stressed by Hamilton and Abbott.<sup>5</sup> In 200 cases of coarctation of the aorta which they analyzed, a congenital bicuspid valve was present in 51 or 25 per cent. Abbott<sup>1</sup> has collected a total of 67 cases of the combination.

The etiology, pathogenesis, and clinical significance of both congenital defects have been dealt with adequately in the literature, especially by Abbott and by Blackford, and need not be considered here.

## CASE REPORT

C. G., white male, aged thirty years, was admitted to the Lenox Hill Hospital, Jan. 10, 1936, complaining of dyspnea, weakness, and palpitation. One year prior to admission, he had suffered from dyspnea and fatigue. These symptoms disappeared after a short period of treatment. Two weeks prior to admission, the above symptoms returned, and in addition, he complained of a dull aching, precordial pain on exertion. He had also suffered from hoarseness and a dry, nonproductive cough for several months.

His previous history was irrelevant except for a hernioplasty performed in 1924 and gonorrhea at the age of twenty years. Syphilis was denied.

*Physical examination* showed an apprehensive, white male, moderately cyanotic and dyspneic. A "brassy" cough was present.

\*From the Medical Service of Dr. Otto M. Schwerdtfeger, Lenox Hill Hospital.

The pupils were slightly irregular but both reacted to light and in accommodation.

There was marked arterial pulsation in the neck and the veins were distended but did not fill from below. A tracheal tug was present. The thyroid gland was not palpable.

The thorax exhibited posteriorly many tortuous pulsating vessels, especially along the vertebral borders of the scapulae and along the lower margins of the ribs. At these sites could be felt a marked systolic thrill and in the posterior interscapular regions, at the level of the third dorsal vertebra, a loud blowing systolic murmur was audible. The internal mammary arteries were not visible. The lungs were resonant throughout. Moist râles were present at both bases.

The heart was moderately enlarged downward and to the left, the apex beat being visible in the sixth intercostal space in the anterior axillary line. Both systolic and diastolic thrills were palpable over the base. A diastolic thrill was also felt at the apex. The aortic sounds were replaced by a harsh, systolic murmur followed by a prolonged, high-pitched diastolic blow which was transmitted downward and to the apex and was best heard at the second left interspace. At the apex, in addition, a loud blowing systolic murmur was audible. The pulse was Corrigan in type, regular, rate 86. The blood pressures in the extremities were as follows: right arm: 160/50; left arm: 190/56; right leg: 108/80; left leg: 104/80. A capillary pulse was present.

The liver and spleen were not palpable. There was an absence of pulsation of the abdominal aorta.

The extremities showed slight cyanosis but no clubbing. There was no edema. The reflexes were physiological.

*Laboratory Data.*—Blood count on admission: Hemoglobin, 94 per cent (Sahli); red blood count, 4,300,000; white blood count, 10,600; polymorphonuclears, 76 per cent; lymphocytes, 13 per cent; monocytes, 11 per cent.

Urinalyses showed a specific gravity range from 1.008 to 1.029, albumin 1 to 2 plus; and red blood cells on only one occasion, two weeks before death.

Blood and spinal fluid Wassermann tests were negative.

Repeated blood cultures revealed the constant presence of *Streptococcus viridans*.

Electrocardiograms taken on several occasions showed variations in the P-R interval from normal to 0.34 second and widening of the QRS complex to 0.12 second at times. The ventricular complex was slurred in all three leads. The P-wave was notched in Leads I and II and frequently inverted in Lead III.

Röntgenograms of the chest revealed an absence of a prominent aortic knob, dimpling of the descending aorta in the left oblique position, and scalloping of the lower margins of the eighth and ninth ribs.

*Course.*—The temperature rose on the day after admission and continued elevated until his death. It was remittent in character and its upper level ranged between 102° and 103° F. His course was uneventful, except for the discomfort incident to the fever, until the eighteenth day, when an episode of pain and tenderness in the left upper quadrant occurred. The spleen was not palpable and no friction rub was audible. Later, occasional petechiae in the conjunctivae appeared, and the finger-pads were painful and tender at times. Microscopic hematuria did not occur until the sixtieth day. Late in the course of the disease, the spleen was palpable. He became progressively weaker, more anemic, and then developed signs of congestive failure with orthopnea, right hydrothorax, and tender, palpable liver. He expired on the eighty-fifth day of hospitalization.

#### AUTOPSY

*Anatomical description.*—The body was that of a well-developed and well-nourished male. The skin and mucous membranes were slightly jaundiced. One petechial hemorrhage was found inside the left lower lid.

On opening the thorax, the heart was seen to be markedly enlarged to the left with some compression of the lung. The right pleural cavity contained about 100 c.c. of clear, amber fluid. The right lung was removed with ease and weighed 775 gm. The left lung was densely adherent to the parietal pleura and weighed 725 gm. Both lower lobes and the posterior half of the right middle lobe showed scattered areas of consolidation.

The pericardial sac contained about 30 c.c. of slightly turbid, pale yellowish fluid. The heart and aorta weighed 800 gm. (Fig. 1). The right auricle and ven-

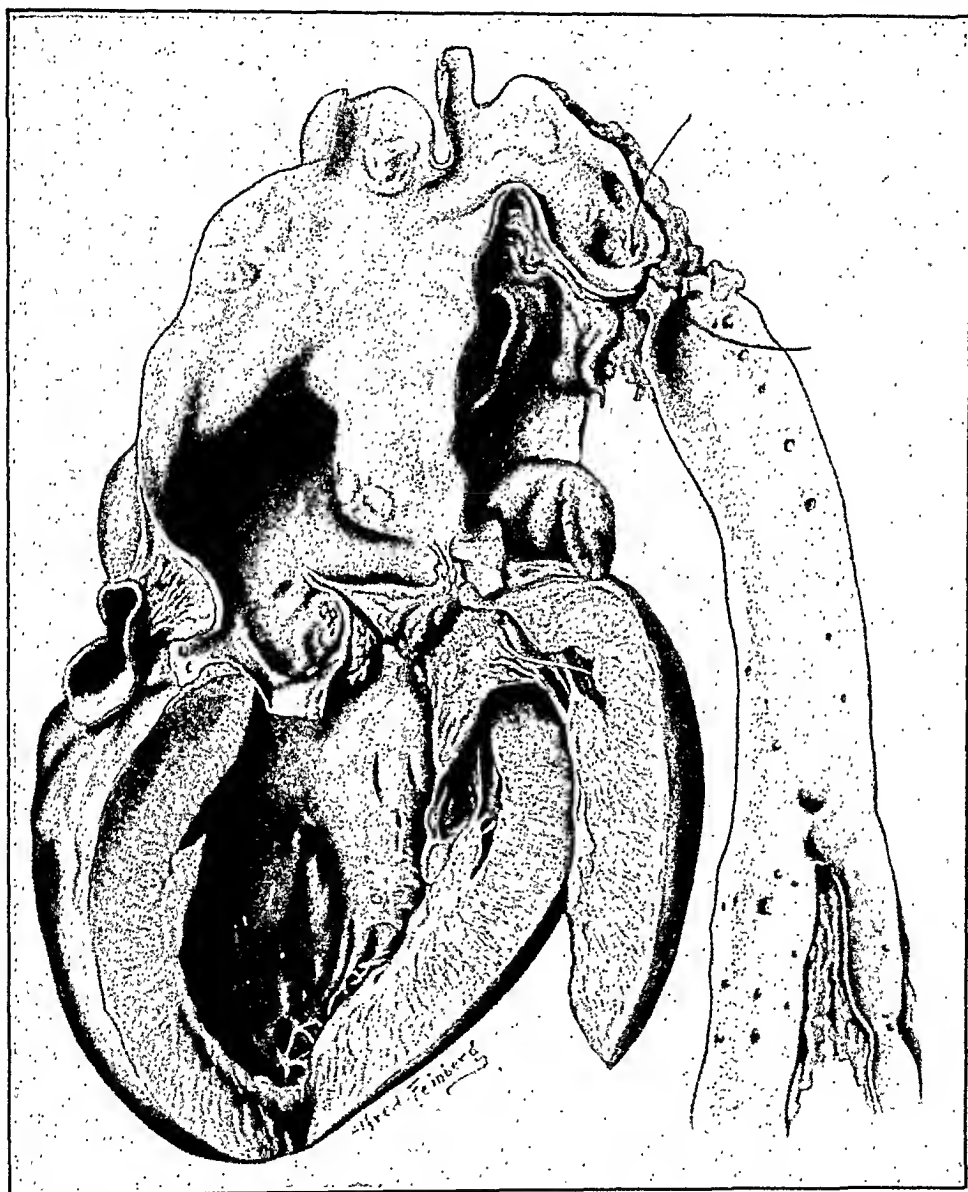


Fig. 1.—Drawing of the left ventricle and aorta showing the bicuspid aortic valve involved by a vegetative endocarditis and the site of the coarctation.

tricle were moderately dilated. The tricuspid valve measured 6 cm. in diameter and the endocardium over the leaflets was smooth and pale gray. The right ventricular wall was 8 mm. thick. The pulmonary valve, artery, and veins showed no gross anatomical lesions. The left ventricle was markedly hypertrophied and dilated and the middle of its anterior wall was 2.6 cm. thick. The papillary muscles were hypertrophied. The mitral valve measured 4 cm. in diameter.

The coronary arteries were dilated and exhibited a few scattered, yellowish, intimal plaques.

The aortic valve exhibited but two complete cusps. One lay posteriorly and somewhat to the right and represented the coronary-free cusp. The other lay anteriorly and slightly to the left. The latter was subdivided at approximately its middle by a shallow ridge. The division of this cusp into right and left anterior cusps was not marked by any indentation on its ventricular surface. Both cusps were partially covered by large friable vegetations. The vegetations almost completely covered the entire length of the coronary-free cusp and extended down on the posterior surface of the aortic cusp of the mitral valve. Only the left half of the other cusp was involved by the vegetations, which had, however, ulcerated through the cusp near its posterior insertion. Where visible the free edges of the cusp were thickened and rounded. Both coronary orifices arose about the level of the origin of the ridge. The left coronary orifice lay approximately in the center of that portion of the sinus of Valsalva between the raphe and the anterior insertion of the double cusp. The right coronary orifice lay close to the insertion of

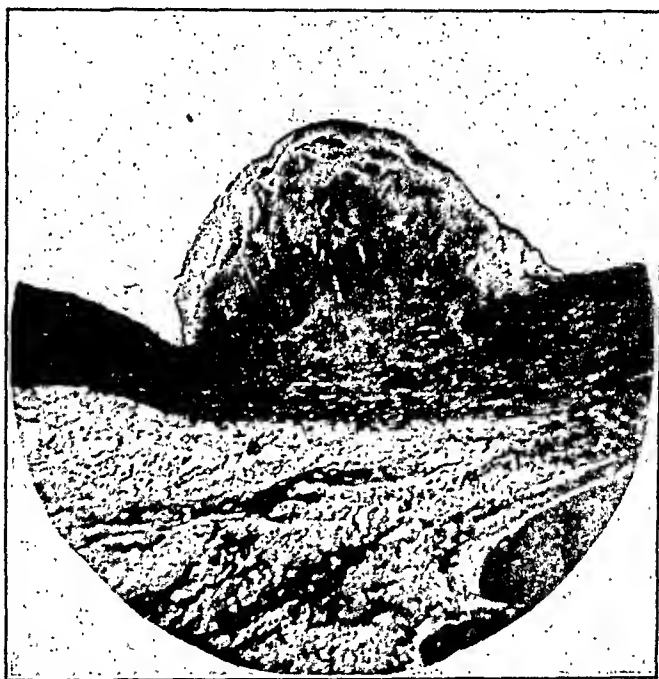


Fig. 2.—Photomicrograph of a section of the raphe of the bicuspid valve ( $\times 15$ ). Weigert's elastic tissue stain.

this cusp, 1.4 cm. from the raphe. The subdividing ridge measured 15 mm. in length, its greatest width located near its center measured 6 mm. and its greatest height measured 5 mm. It was pearly gray and smooth and widened near its insertion to assume a bifid appearance and to fuse with the cusp, 8 mm. below its free edge. There was a small, mottled, yellowish, nodular thickening of the raphe at its origin. The coronary-free cusp measured 3.8 cm. and the double cusp, 4.2 cm. in length.

The aorta rapidly enlarged after its origin to form an aneurysmal dilatation which bulged outward and to the right. Its wall was markedly thinned. Immediately above the valve, the circumference of the aorta was 9.3 cm. and its greatest width at the aneurysm was 13.1 cm. At the level of the innominate arteries, it had narrowed to 4.8 cm., at the left carotid, to 2.1 cm. and at the left subclavian, to 1.8 cm. Beyond the left subclavian there was a sudden narrowing of the aorta to where it terminated at the level of the closed ligamentum arteriosum, 12.6 cm.

above the aortic valve. The descending aorta, 2 cm. below the stricture, had widened to 3.5 cm. The branches from the arch as well as the abdominal branches were dilated. The internal mammary arteries averaged 8 mm. in diameter. Above the anterior commissure and the coronary-free cusp were several raised, yellowish, arteriosclerotic plaques. There were several such plaques about the orifice of the right innominate and in the narrow termination of the aorta.

The parietal and visceral abdominal peritoneum were grossly normal. The liver was enlarged, weighing 1,975 gm. and extended 8 cm. below the costal margin. On section, it was yellowish pink in color and the parenchymal markings were indistinct. The spleen was enlarged to about twice its normal size, weighed 300 gm. and was covered by a smooth, dark bluish capsule. It was soft in consistency. On section, the pulp was softened and congested and the corpuscles were prominent. The kidneys were slightly enlarged, each weighing 200 gm. The capsules stripped with ease and the surface was smooth and congested. On section, the markings were indistinct. The other organs were grossly normal.

The anatomical diagnosis was: hypertrophy and dilatation of the left heart; bicuspid aortic valve; vegetative endocarditis involving the aortic and mitral valves; coarctation of the aorta (adult type); aneurysm of the ascending aorta; moderate arteriosclerosis of the aorta; right hydrothorax; left chronic adhesive pleuritis; bilateral bronchopneumonia; congestion and fatty degeneration of the liver; acute splenic tumor; congestion of the kidneys; petechial hemorrhage in the conjunctiva of the left lower eyelid.

*Histological Examination.*—Serial sections through the aortic half of the subdividing ridge, including the adjacent portion of the sinuses, were stained with hematoxylin-eosin and Weigert's elastic tissue stain (Fig. 2). These showed the aorta adjacent to the ridge to be composed of the usual three layers. The intima exhibited a rather well-defined internal elastic lamina. The inner two-thirds of the media had an abundance of elastic fibrils arranged in the classic pattern, while the outer third was composed of fibromuscular tissue and contained very few elastic fibrils. As the ridge was approached, the elastic portion of the media became narrowed and condensed. The intima was continued over the ridge, as was the major portion of the condensed layer of the media, both being so fused that a definite sub-endothelial layer or internal elastic lamina could not be distinguished. The rest of the condensed layer was broken up and lost in the fibromuscular tissue at the base of the raphe. The body of the ridge was composed of irregular whorls of hyaline, fibrous tissue which was continuous with the outer third of the medial coat. Small collections of elastic tissue fragments were present near the surface of the ridge.

Sections through the aorta showed a moderate fibrosis of the media. In the floor of the aneurysmal dilatation it was markedly thinned.

The heart muscle showed occasional small collections of leucocytes and moderate congestion. The lungs showed congestion, edema, and bronchopneumonia. The liver was congested and exhibited marked fatty degeneration. The spleen was deeply congested. The glomerular tufts of the kidneys were swollen and some were partially adherent to the capsule. A moderate tubular degeneration was present.

#### COMMENT

The case here reported is a typical example of coarctation of the aorta of the adult type exhibiting the classical clinical and roentgenographic findings which made possible a diagnosis during life. Its clinical importance does not end here as it illustrates the fact that a diagnosis of an associated congenital bicuspid aortic valve could also have been made with a great degree of certainty. The frequency



of its combination with coarctation of the aorta has already been alluded to. The tendency of the malformed valve to undergo a chronic sclerotic process with resultant thickening, calcification, and deformity and the predilection for this chronic lesion to become the seat of acute or subacute infectious endocarditis are well known. Lewis and Grant<sup>3</sup> have shown that subacute bacterial endocarditis is the cause of death in a great majority of the cases of bicuspid aortic valve. The occurrence, therefore, of a subacute bacterial endocarditis involving the aortic valve in a case of coarctation of the aorta, should make it highly presumptive that a bicuspid aortic valve is also present.

The absence of embolic phenomena in the abdominal viscera and the lower extremities is of interest and is easily explained by the anatomical conditions present.

Pathologically, the bicuspid valve conforms in every way to the macroscopic criteria for a congenital bicuspid valve as first formulated by Osler<sup>2</sup> and then by Lewis and Grant<sup>3</sup> and to the distinctive microscopic features as described by the latter. The microscopic criteria are naturally more important, as the frequency of superimposed degenerative or infective processes on the valve make the differentiation between those of congenital origin and those due to postnatal inflammatory fusion extremely difficult on gross appearance only.

The aneurysmal dilatation of the aorta is the usual concomitant of coarctation and is a common cause of death.

#### SUMMARY

A case of coarctation of the aorta is presented which was associated with a congenital bicuspid aortic valve on which was superimposed a subacute bacterial endocarditis. A histologic examination of the raphe of the malformed cusp is included.

#### REFERENCES

1. Abbott, M. E.: *Libman Anniv.* Vol. 1: 6, 1932.
2. Osler, W.: *Tr. Assn. Am. Physicians.* 1: 185, 1886.
3. Lewis, T., and Grant, R. T.: *Heart* 10: 31, 1923.
4. Blackford, L. M.: *Arch Int. Med.* 41: 702, 1928.
5. Hamilton, W. F., and Abbott, M. E.: *AM. HEART J.* 3: 381, 1928.

# ANEURYSM OF THE ARCH OF THE AORTA DUE TO PERSISTENCE OF A PORTION OF THE DUCTUS ARTERIOSUS IN AN ADULT\*

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**I**NCOMPLETE closure of the ductus arteriosus is not an uncommon post-mortem finding in infants who die during the first weeks of life. Persistence of only a portion of the duct of Botalli in adults, however, is exceedingly rare; the only previously reported case available in the literature is that of Hebb.<sup>1</sup>

## REPORT OF CASE

J. O. (Hospital No. 74509, Med. No. 39173), a fifty-six-year-old married Scotch upholsterer, with an irrelevant past history, entered the Peter Bent Brigham Hospital for the second time on Feb. 3, 1932, complaining of increasingly severe dyspnea on exertion of three and one-half years' duration. He had also had a severe dry hacking cough, orthopnea, and slight swelling of the ankles beginning in June, 1931, requiring admission to the hospital at that time. Hospitalization resulted in only temporary improvement. Physical examinations at the time of both admissions to the hospital were essentially the same, the principal physical findings consisting of respiratory difficulty, cyanosis, enlargement of the heart to percussion, a harsh apical systolic murmur, auricular fibrillation, numerous râles in both lungs, slight enlargement of the liver, and slight edema of the ankles. The blood pressure was 230 mm. of mercury systolic and 140 mm. of mercury diastolic. Ophthalmoscopic examination revealed absence of disc margins and physiological cupping, and the presence of marked vascular changes and many patches of hemorrhage and exudate in both eyegrounds. During the two weeks of his second hospital stay he had repeated attacks of fever, slight jaundice, tachycardia, and exacerbation of dyspnea. He died suddenly on Feb. 19, 1932.

Autopsy (No. A32-19) was performed ten hours post mortem.

A cone-shaped sacculaton, measuring 1 cm. in diameter at its base and 1 cm. in depth, was found springing from the wall of the aorta at the point at which it crossed the pulmonary artery. The apex of the cone pointed toward the pulmonary artery, and was connected with it by a fibrous cord 1 cm. long. The attachment of the fibrous cord was marked by a dimple 2 mm. in diameter in the intima of the pulmonary artery. A mottled greyish yellow, granular, adherent thrombus filled the sacculaton and extended 3 mm. beyond its orifice. On microscopic examination of the aneurysm, capillaries and young fibroblasts were seen growing into the base of the thrombus from the much thickened subjacent intima. Endothelium was growing from the adjacent portion of the intima of the aorta over the top of the thrombus at its edges. The cord running from the aneurysm to the pulmonary artery was found to consist of dense collagen containing a few clusters of round cells. The intima of the pulmonary artery was thickened at the point of attachment of the fibrous cord, with which it was continuous. Paralleling this fibrous cord were small bundles of smooth muscle.

The heart weighed 550 grams; the thickness of the wall of the left ventricle was 14 to 16 mm. and that of the right, 2 to 4 mm. A mural thrombus filled the left auricular appendage; another was situated on the posterior wall of the left auricle, and a third, 1 cm. in diameter, overlay an area of recent infarction of the same

\*From the Pathological Laboratory, Peter Bent Brigham Hospital.

size in the apex of the right ventricle. The left lung contained twelve areas of recent hemorrhagic infarction. The other important findings consisted of moderate generalized arteriosclerosis, moderate arteriolar medial hyalinization and hypertrophy in the heart, brain, and all the abdominal viscera, marked congestion of all the organs, marked central necrosis of the liver, small areas of hemorrhage in the brain, pancreas, and bladder, slight vascular nephritis, chronic cholecystitis, and evidence of a small amount of acute and chronic inflammation of the pancreas. One medium-sized artery in the pancreas was filled with an organizing thrombus.

#### DISCUSSION

Complete patency of the ductus arteriosus is a congenital anomaly not uncommonly found in adults. Incomplete closure of the ductus in an adult, however, has heretofore been noted only once. The only

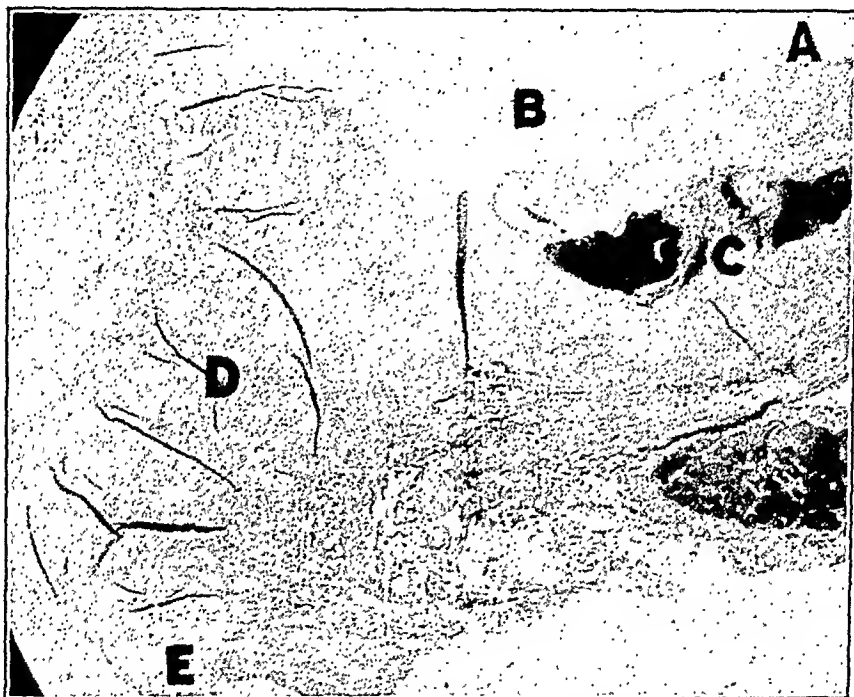


Fig. 1.—Section through the incompletely closed ductus arteriosus. A. Aorta. B. Aneurysm. C. Thrombus. D. Obliterated portion of ductus arteriosus. E. Pulmonary artery.

other case in the literature, that described by Hebb,<sup>1</sup> was a man of forty years of age who died of pulmonary tuberculosis. In him the patent portion of the ductus was described as follows: "Just beyond and opposite the subclavian is a circular aperture  $\frac{1}{8}$  inch across leading into a spheroidal aneurysm about the size of a walnut. It was entirely filled with firm laminated clot." This structure abutted against the pulmonary artery and the left bronchus. Other congenital anomalies were also found post mortem in Hebb's case; these consisted of complete obliteration of the left branch of pulmonary artery and marked stenosis at its origin of the right.

The reason for partial persistence of the ductus arteriosus in adults cannot be stated. It is possible that the findings in such cases repre-

sent a stage in a very much delayed process of closure. It is to be noted that in Hebb's case, as well as in the one here reported, an increased pulmonary arterial pressure existed, due in the former to marked pulmonic stenosis and in the latter to severe left ventricular failure. Possibly the gradual increase in pulmonary arterial pressure which occurred in both cases finally became sufficient to retard the flow of blood through a patent ductus from the aorta, thereby favoring closure.

In Hebb's case, as well as in the one here reported, the persistent portion of the ductus existed as a small, thrombosed, saccular aneurysm springing from the wall of the aorta. The presence of this anomaly in both cases was entirely unsuspected during life. Its presence cannot be diagnosed since it gives rise to no specific signs or symptoms. It is conceivable, however, that such an aneurysm might become clinically important should a portion of its thrombus become dislodged and give rise to peripheral embolic manifestations. The possible relation of the thrombus in the small pancreatic artery to the thrombus in the persistent portion of the ductus arteriosus in the case here reported should be noted.

#### REFERENCE

1. Hebb, R. G.: Aneurysm of Ductus Arteriosus and Atheroma of Pulmonary Artery, *Tr. Path. Soc. London* 44: 45, 1893.

# Department of Reviews and Abstracts

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## Selected Abstracts

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Graybiel, Ashton, and White, Paul D.: Diseases of the Heart. A Review of Some Contributions Made During 1936. *Arch. Int. Med.* 59: 892, 1937.

This annual review of the literature pertaining to diseases of the heart discusses briefly and clearly the important contributions made during the year 1936. The value of such a review is considerable and should be included in one's reading on this subject. Special attention has been given this year to foreign medical reports.

H. McC.

Gross, Louis, Blum, Lester, and Silverman, Gertrude: Experimental Attempts to Increase the Blood Supply to the Dog's Heart by Means of Coronary Sinus Occlusion. *J. Exper. Med.* 65: 91, 1937.

Sudden occlusion of the left anterior descending branch approximately 2 cm. below the ostium of the left circumflex coronary artery in the dog's heart produces a mortality rate of approximately 50 per cent. In dogs weighing approximately 15 kilograms surviving more than twenty-four hours (average one week), an infarction is produced which almost invariably measures 5 by 5 cm. on surface. Following coronary sinus obturation, such secondary sudden occlusion of the left anterior descending branch is followed either by no infarction or by a reduction in the size of the infarct. The success of the procedure, quite apart from the mortality rate, depends upon the completeness of the coronary sinus obturation. On the other hand, sudden and complete coronary sinus obturation by itself is associated with a high operative mortality and apparently does not affect the mortality rate following subsequent sudden left anterior descending branch occlusion. Partial persistent obturation of the coronary sinus, however, is in itself associated with a low operative mortality. Furthermore, its experimental production in dogs appears to lower the mortality rate following subsequent sudden occlusion of the left anterior descending branch and to diminish the extent of the infarction.

In the introduction to this report it was pointed out that there are three important desiderata to the problem of improving the coronary circulation in the human heart. The findings herein reported fulfill these requisites to an encouraging degree. It has been shown that, following the outlined procedures, a functional increase in the blood supply to the heart can be produced in a significant proportion of experimental animals, this varying with the nature of the experimental procedure. The manipulation is simple, can be performed in the dog within approximately twenty minutes, and does not lead to appreciable pericardial adhesions. Increase in the nutrition of the myocardium is noted one week after the experimental procedure. Although no experiments employing sudden left anterior descending coronary branch occlusion were carried out sooner than one week, there is available anatomical evidence that within possibly twenty-four hours after coronary sinus occlusion a dilatation of the vascular bed occurs. In subsequent experiments attempts will be made to determine whether this early vascular dilatation is adequate to compensate for subsequent sudden left anterior descending branch occlusion.

A discussion is given of the results following various coronary sinus occlusion procedures in which it is indicated that it is desirable to produce a partial or gradual occlusion in order to lower the mortality rate of the initial procedure as well as of the subsequent sudden arterial occlusion. Experiments thus far reported on cardiopexy operations are lacking evidence that they are associated with appreciable improvement in the vascular nutrition of the myocardium.

AUTHOR.

Gross, Louis, Mendlowitz, Milton, and Schauer, Gerhard: Hemodynamics Following Experimental Coronary Occlusion in Dogs. *Proc. Soc. Exper. Biol. & Med.* 35: 446, 1936.

Following left anterior descending coronary branch ligation in the open or closed chest, there is an immediate appreciable fall in average cardiac output and also a delay in cyanide circulation time. Control experiments indicate that these changes are directly attributable to the ligation of the coronary branch. Following these procedures, there are no other appreciable changes in the hemodynamics studied.

AUTHOR.

Herbst, R., and Manigold, K.: The Reaction of the Circulation and Respiration in Anoxemia. *Arbeitsphysiol.* 9: 166, 1936.

It was found that, when the pressure was reduced to one-half atmosphere in a low pressure chamber, no change in circulation could be demonstrated in normal recumbent persons. With pressures lower than this, the pulse accelerated (approximately as a logarithmic function of the pressure). At low pressures, systolic and pulse pressures rose and an increase in cardiac stroke volume occurred in some instances. At very low pressures collapse occurred, with the pulse slowing and pressures and stroke volume decreasing. Oxygen inhalation quickly relieved the symptoms. Respirations during the lowering of pressure in the chamber became slower and deeper.

L. N. K.

Werle, E., and Hürter, J.: Ornitho-Kallikrein I. *Biochem. Ztschr.* 285: 175, 1936.

From the pancreas and other organs of birds (pigeon, hen, and goose) an extract was obtained which lowers the blood pressure in birds but not in mammals (cat and dog). Mammalian *Kallikrein*, which lowers the blood pressure in mammals, has no effect on birds.

L. N. K.

v. Euler, U. S.: Observations on Substance P, the Atropinfast, Intestine Stimulating and Blood Vessel Dilating Substance Obtained From the Intestines and the Brain. *Arch. f. exper. Path. u. Pharmakol.* 181: 181, 1936.

This is a continuation of the study of a new substance isolated by Euler and Gaddum. Trypsin inactivates the substance, indicating its albuminose character. It lowers blood pressure and stimulates the gut and uterus. Since it is found in biodialysates of rabbit gut, it presumably plays an important rôle in the movements of the gut normally.

L. N. K.

Klatsiecki, A.: The Flow of Blood in the Aortic Arch. *Ztschr. f. Biol.* 97: 1, 1936.

A modified photohemotachometer of Cybulski's was used in a dog, and, surprisingly, the author found that there is no systolic acceleration of blood flow in the aorta when the vessel is permitted to expand and the rate of the dog's heart is normal. When the pulse rate is slowed, a pulsatory variation in linear velocity of flow occurs during the heart cycle. At very slow rates the velocity varies from 0 mm. rate in diastole to 400 mm. per second in systole.

L. N. K.

Weiss, Soma, and Wilkins, Robert W.: The Nature of the Cardiovascular Disturbances in Vitamin Deficiency States. *Tr. A. Am. Physicians*, p. 341, 1936.

Dysfunction of the cardiovascular system may develop as the result of an unbalanced food intake, particularly lacking in vitamin B. The condition may affect a normal or a previously diseased heart. The cardiovascular manifestations here described depend partly on changes in the nervous system and partly on changes in the myocardium and the vascular system.

Simple tachycardia, vagus reflex irritability with bradycardia or with asystole and syncope, right-sided and left-sided heart failure, peripheral arteriolar dilatation, and vasomotor collapse with vascular constriction were observed in various combinations.

With rest and a dietary regime the circulatory disturbances disappeared rapidly in one group and slowly in another group. Sudden death as a result of vasomotor collapse also occurred.

In 38 cases the electrocardiograms were normal in but 3 instances. The main abnormalities were changes in the T-waves and low amplitude and prolongation of the electrical systole (Q-T). Under therapeutic measures these changes usually disappeared.

The histological changes in the cardiac muscle and conductive systems were identical with those described by Wennekebach in beriberi heart of Java. These changes, however, are not specific or characteristic of hearts in deficiency diseases.

The coexistence of polyneuritis and the cardiovascular disturbances described serves as additional evidence for the vitamin B deficiency theory of "alcoholic polyneuritis."

Cardiovascular manifestations associated with vitamin B deficiency are more than mere sporadic manifestations in the northeast and probably in other sections of the United States. The condition here described may well bear pertinently on the behavior and the mortality rates of alcoholic and nonalcoholic patients with vitamin B deficiencies (beriberi and pellagra) in the presence of infection, in association with high metabolic rates in general, and under surgical conditions. The therapeutic implications under these conditions are discussed.

AUTHOR.

Parkinson, John, and Hoyle, Clifford: The Heart in Emphysema. *Quart. J. Med.* 6: 59, 1937.

Eighty patients suffering from a high grade of emphysema were investigated, chiefly in regard to the cardiovascular system and particularly with reference to the size and shape of the heart as judged by radiology.

The cardiac factor in emphysema alone is seldom pronounced except late in the disease, and then not always, unless there is also a cardiac lesion of another sort. A complicated etiology is so common that it was demonstrable in more than half of this series, and the complication was predominantly hypertension. It may be

said that cardiac symptoms and signs in emphysema are more likely to be due to hypertension than to the direct effect of emphysema on the heart.

Clinical evidence is an uncertain guide to involvement of the heart in either pure emphysema or when this is combined with other cardiovascular disease. Cardiac and pulmonary symptoms are similar, and the physical signs in emphysema indicative of a cardiac element are admittedly few. In particular there is no guide to cardiac enlargement, and as this is a proof that the heart is implicated, we are dependent on radiology, except in late examples where edema is proof enough that the heart is involved. Electrocardiographic evidence is disappointing, for there is right ventricular predominance in a small proportion only; its chief value is to provide other evidence of a complicating myocardial (coronary) disease, e.g. a bundle-branch lesion.

The most frequent and radiological change in the cardiac involvement of emphysema is enlargement of the branches of the pulmonary artery at the hila (about 46 per cent). In the anterior view the enlarged pulmonary or middle are is sometimes obscured by its large left branch. Localized enlargement of the heart is the second main proof that the heart is implicated in emphysema, and it is demonstrable in over one-third (about 40 per cent). It concerns most often the conus pulmonalis of the right ventricle (about 41 per cent), and in about one-half these the body of the right ventricle also, best seen in the left (II) oblique and right (I) oblique positions, respectively. Enlargement of the right auricle is not common (about 14 per cent).

Enlargement of the left ventricle (about 30 per cent) and of the left auricle (about 1 per cent) is dependent upon the coexistence of other cardiovascular disease, for in pure examples of emphysema it does not occur, unless, perhaps, in the late stage of congestive failure. Systemic hypertension is the almost invariable cause of the left ventricular enlargement when this is found; a few others have myocardial (coronary) disease, e.g., with bundle-branch block. Enlargement of the left auricle was found once only, and that in the sole instance of auricular fibrillation. The infrequency of enlargement of the right auricle and the rarity of enlargement of the left auricle can be related to the freedom from auricular fibrillation and to the admitted rarity of failure at all from emphysema alone.

The heart as a whole is not enlarged in uncomplicated cases of emphysema. Great enlargement of the right heart is rare, being seen in four only. In none of these was there a sabot appearance. About one-third of patients have no enlargement at all and no changes in the pulmonary vessels radiologically. The small and droplike heart shadow, though so often held to be characteristic of emphysema, is in our experience only seen occasionally.

These results from the use of x-rays now permit recognition in life of the features of enlargement long known to morbid anatomists. They go further in that most of these traditional records are largely diminished in value by the inclusion of unrecognized associated hypertension or myocardial disease. In pure emphysema it is the outflow tract of the right ventricle (Kirsch) extending from the apex to the pulmonary artery, which is earliest affected by enlargement and manifested by prominence of the conus. Later the body of the right ventricle is also involved, and this is represented by right ventricular prominence in the left (II) oblique position. These are the changes in the heart characteristic of pulmonary hypertension. Cardiac failure from emphysema alone is surprisingly rare; and, when it occurs, it is with normal rhythm and edema, and as a very late event that is almost invariably terminal. Recurrent attacks of failure are almost unknown. Examples of failure apparently due to emphysema are most often explained by associated cardiovascular disease, usually hypertension, and in such, failure can be recurrent. The differential diagnosis, especially from mitral stenosis, congenital heart disease, and the heart in patients with goiter, is briefly discussed.

AUTHOR.



Van Nieuwenhuizen, C. L. C., and Hartog, H. A. P.: Chest Leads in Electrocardiography. *Arch. Int. Med.* 59: 448, 1937.

Data obtained from the chest lead derived as a routine method are discussed on a basis of 1,500 tracings. In coronary thrombosis the chest lead often offers the only electrocardiographic diagnostic evidence. The importance of the chest lead for the differential diagnosis of acute intrathoracic or abdominal deviations with coronary thrombosis is pointed out. The chest lead may be of much value also in reaching a diagnosis in a case of gradually arising myocardial infarction. The tracings obtained in coronary thrombosis are divided into two groups, one of which was caused by anterior infarction and the other possibly by posterior or septal infarction.

It is not improbable that these last curves indicated an atypical bundle-branch block. But there still remains the question whether the cause is not an insufficiency of the blood supply by the posterior coronary artery. The latter form of tracing was seen in one case of rheumatic myocarditis. The history of a patient in the first group usually records an acute attack; that of a patient in the second group usually bears no record of a sudden attack of pain or oppression. This is the reason these myocardial changes often escape clinical observation. Next the clinical significance of an abnormally deep T-wave (deeper than -10 mm.) is pointed out. With a few exceptions such a wave is always found in organic disease of the heart. In cases of mitral stenosis, however, the T-waves in the standard leads are strongly positive; in other groups (hypertension, chronic nephritis, and aortic defects) all or part of them are abnormal. The hypothesis is advanced that the deep T-wave in mitral stenosis is the result of a difference in the position of the heart; in the other groups this might be the result of myocardial disease. A deep T-wave is found also in bundle-branch block. Then, however, the ventricular complex is very high and large, in analogy to the diphasic ventricular complexes in the other leads.

Finally the importance of the chest lead in making an electrocardiographic diagnosis of diffuse myocardial damage is demonstrated either as a support for the third lead or as the sole criterion. Here the T-wave may be shallow, diphasic, or positive. Other factors which influence the shape of the T-wave in the chest lead are digitalis and a longitudinal position of the heart, especially in children.

AUTHOR.

Ludwig, H., and Bener, A.: Audible Auricular Sounds in Auricular Flutter. *Klin. Wehnschr.* 15: 271, 1936.

A case of flutter of the auricles is reported in which each auricular contraction is accompanied by an audible sound, best heard in the second and third intercostal spaces in the left parasternal line. This was recorded photographically. The flutter rate was 250 per minute. There was total and later irregular A-V block and also intraventricular block. The heart was large, and there was cardiac failure. A loud systolic murmur was present at the apex, and a loud diastolic murmur was heard over the lower sternum.

L. N. K.

Feil, Harold: Preliminary Pain in Coronary Thrombosis. *Am. J. M. Sc.* 193: 42, 1937.

Fifteen cases of coronary thrombosis, with myocardial infarction in fourteen, have been observed with preliminary mild anginal attacks preceding the clinical picture of thrombosis by hours or days—usually from twelve to forty-eight hours. This pain is not dependent on effort or emotion, is more or less continuous, and is of an oppressive and burning character. The electrocardiogram was normal in two of five patients whose records were taken during this preliminary pain. The abnormal changes in the other cases are described. A gradually forming thrombus in a

stenosed coronary artery appears to be the most probable explanation for the occurrence of the preliminary pain. The possibility of the development of a coronary artery thrombus should be suspected in patients who have persistent retrosternal pain, not related to effort, emotion or digestion, especially when hypertension or the anginal syndrome has been previously noted. Effort should be made to improve coronary artery flow. Urging of fluids (to avoid dehydration), administration of aminophyllin, alcohol, and nitrites, moderate restriction of physical activity, mental rest, and restriction of insulin and tobacco are indicated.

AUTHOR.

Kisch, F.: Statistical Observations on Life Expectancy in Coronary Thrombosis. *Klin. Wchnschr.* 15: 440, 1936.

The circulatory collapse after coronary thrombosis was followed by death in 23.5 per cent of the cases, the mortality being higher in women than in men. In many cases of coronary thrombosis, the blood sedimentation time may be of prognostic value in determining the progress of the infarct. A characteristic electrocardiographic deviation is compatible with several years of life.

L. N. K.

Thompson, William Paul, and Levine, Samuel A.: Note on the Duration of Symptoms and Age at Death in Chronic Rheumatic Valvular Disease, Especially in Tricuspid Stenosis. *Am. J. M. Sc.* 193: 4, 1937.

The authors have found that patients with tricuspid stenosis, in spite of the fact that death occurs at a comparatively early age, are able to tolerate their symptoms considerably longer than are those patients in whom the tricuspid valve is not involved. The average figures are, therefore, somewhat paradoxical and contrary to what one might expect. We have attempted to point out, however, that in tricuspid stenosis the symptoms and signs are not due wholly to myocardial failure and that they are due in part to mechanical obstruction to the normal diastolic filling of the heart, so that this apparent paradox is in part, at least, explained.

It is believed that these figures contribute two important clues to the diagnosis of tricuspid stenosis: first, the appearance of symptoms at an early age in patients with chronic rheumatic valvular disease and, second, an ability to carry on with such symptoms for an unusually long time, particularly when the prominent features are enlargement of the liver and ascites. If these features cause us to suspect tricuspid stenosis, we are then one step nearer the goal of making accurate ante-mortem diagnoses.

AUTHOR.

Reichel, H.: Bacterial Cultures From the Blood in Endocarditis Lenta. *Klin. Wchnschr.* 15: 642, 1936.

In some cases of endocarditis lenta liquid media are required to demonstrate positive blood cultures. With proper precautions growth will occur in ordinary nutrient broth and macroscopic colonies will appear.

L. N. K.

Cushing, E. H.: Diverticulum of the Pericardium. *Arch. Int. Med.* 59: 56, 1937.

Thirty-nine cases of diverticulum of the pericardium have been described in the literature, and one additional case is reported here.

This case is the first described in which a pericardial diverticulum has presented on the anterior wall of the chest. The diagnosis was confirmed by injecting air

into the subcutaneous mass and finding air within the pericardial cavity. The roentgenographic findings were typical of those in the cases described by Kienbock and Weiss and by Jansson. The diagnosis of calcified tuberculous pericarditis was confirmed by the demonstration of tubercle bacilli in the pericardial fluid obtained by aspirating the diverticulum and by the death with tuberculosis of guinea pigs inoculated with the fluid.

AUTHOR.

Gross, Louis: So-Called Congenital Bicuspid Aortic Valve. *Arch. Path.* 23: 350, 1937.

A description is given of the bicuspid aortic valve as observed in sixteen adult hearts, eight of which presented the classic macroscopic criteria described by Osler as indicating congenital origin of the malformation and eight of which failed in one respect or another to fulfil these criteria. These hearts presented no associated developmental abnormalities in this respect, resembling previously described adult hearts with so-called congenital bicuspid aortic valves. Strategic cardiac sites and serial sections of the commissures were examined microscopically. Faulty inversion of the commissure as described by Lewis and Grant was found in only two of the sixteen hearts. It was shown that in the majority, apart from the obvious secondary lesions (bacterial endocarditis, syphilis) and degenerative disease (calcific sclerosis of the aortic valve—Mönckeberg type), there were stigmas which strongly implied an associated, generally extinct, rheumatic process. Evidence is presented which supports the hypothesis that a degenerative process (Mönckeberg type) in the minority of instances and a rheumatic process in the majority of instances lead to the formation of the so-called congenital bicuspid aortic valve in the adult. The pathogenesis of the lesion on a rheumatic basis is described, and attention is drawn to the compatibility of this view with the predisposition of the valve with this deformity to subacute bacterial endocarditis. A discussion of the findings leads to the conclusion that Osler's macroscopic criteria are inadequate and do not necessarily indicate a congenital lesion. Attention is directed to the conspicuous differences between bicuspid aortic valves occurring in children and those found in adults. It is suggested that the microscopic criteria offered by Lewis and Grant for the establishment of such a lesion as congenital should be verified by study of serial sections in a representative number of cases in which the bicuspid condition of the aortic valve is of indisputably congenital developmental origin. Such a condition appears to occur considerably more frequently in infants than in adults and is invariably or almost invariably associated with other developmental cardiac defects. For these reasons it is suggested further that a bicuspid aortic valve occurring in an adult should be considered as congenital only when associated with other congenital malformations of the heart. A bicuspid aortic valve not so associated found in adult life should be designated merely "bicuspid valve."

AUTHOR.

McBroom, Josephine, Sunderland, Douglas A., Mote, John R., and Jones, T. Duckett: Effect of Acute Scurvy on the Guinea-Pig Heart. *Arch. Path.* 23: 20, 1937.

Acute scurvy in the guinea pig produces degenerative changes in the cardiac valves and myocardium as well as definite proliferative lesions along the line of closure of the valves. These lesions are equally prevalent and severe in total scurvy whether or not there is superimposed infection.

A deficiency of vitamin C, as shown by Wolbach and Howe and by Wolbach, prevents the adequate formation and maintenance of intercellular substance. It may be expected, therefore, that in regions of strain and stress degenerative lesions may occur and that a proliferative reaction may take place in an attempt at repair. It is as such that the lesions produced in the present study are interpreted.

The complete gross and microscopic pathological changes of rheumatic fever are obviously dissimilar from those of scurvy, even though in some of the microscopic lesions of the valves in both conditions there are certain points in common: a sub-endothelial proliferative reaction with a cellular infiltration and a collagen change. There is also damage to the vascular system in both conditions, but the identity of this injury has not been demonstrated. Although scurvy may indirectly be a factor in lowering the general resistance of the body to infection, there is as yet no evidence that rheumatic fever and scurvy are the same disease, or that there is a direct causal relationship between the two, even with infection by the hemolytic streptococcus complicating the latter. The lesions in the guinea pig heart described by Rinehart and Mettier may be produced by acute scurvy alone and may be interpreted as an attempt at repair of lesions caused by physiological stress on a tissue weakened by acute scorbutus.

AUTHOR.

Bourne, Geoffrey: Acute Rheumatic Meningitis. Brit. M. J. 2: 1017, 1936.

A case of acute rheumatic meningitis is described. A man aged thirty-four years was admitted because of severe rheumatic fever in characteristic form. He developed pericarditis with extensive myocardial injury. After about two weeks there were meningeal signs, and the spinal fluid showed increased pressure with 78 cells. He made an uninterrupted but slow recovery. The central nervous system signs disappeared within about ten days, but the pulse due to the heart block remained for four or five weeks.

It is suggested that for the development of acute meningitis during acute rheumatism some secondary factor such as alcoholism is necessary.

AUTHOR.

Nemet, Geza, and Rosenblatt, Milton B.: Cardiac Failure Secondary to Chronic Pulmonary Tuberculosis. Am. Rev. Tuberc. 35: 713, 1937.

A study of the 71 patients who came to necropsy on the Tuberculosis Division of the Montefiore Hospital during a period of one year revealed 33 instances (46.5 per cent) of right ventricular hypertrophy.

None of the 33 cases was associated with any significant coronary artery disease, valvular disease, or hypertension. There was one instance of antecedent hypertension in a patient with hypertrophy of both ventricles.

Despite enlargement of the right ventricle, the hearts, in general, were smaller than normal.

The duration of the pulmonary disease in these patients did not differ from that seen in all types of tuberculosis patients. All the cases had extensive bilateral involvement and one-third showed definite hematogenous lesions.

Recapitulation of the most significant symptoms revealed the occurrence of dyspnea 30 times (90.9 per cent); cyanosis 23 times (69.6 per cent); hepatomegaly 14 times (42.4 per cent); and peripheral edema 15 times (45.4 per cent). Inconsistencies between the degree of venous distention and venous pressure were noted.

There were too few electrocardiographic studies from which to draw any conclusions. However, review of the literature reveals that right axis deviation with inversion of the T-wave in the second and third leads may be considered indicative of right ventricular enlargement.

Eleven of the 33 cases (33.3 per cent) were recognized during life as having heart disease; in the remaining 22 (66.7 per cent) the diagnosis was entirely post mortem.

It is felt that the inability to distinguish clinically between pulmonary insufficiency and cardiac insufficiency was largely responsible for the low percentage of diagnoses. Dyspnea, cyanosis, venous distention, hepatomegaly, and even edema may be attributable to causes other than cardiac failure in the patient with chronic pulmonary tuberculosis.

The duration of life after cardiac failure had occurred was relatively brief and depended considerably upon the character of the underlying pulmonary process.

The cardinal sign of right ventricular failure is enlargement on fluoroscopy or on the x-ray film. Demonstration of this sign will be facilitated, especially in the early stages, by detailed and frequent studies.

AUTHOR.

Hában, G.: Aneurysms of All Three Sinuses of Valsalva. *Ztschr. f. Kreislauforsch.* 29: 74, 1937.

In the case reported there was evidence post mortem of syphilitic involvement of the valves. The author, however, believes that a congenital structural weakness played a subsidiary rôle in aiding the syphilis to produce the changes.

L. N. K.

Fuchs, F.: Effect of Denervating the Kidney on Blood Pressure. *Wien. klin. Wchnsehr.* 49: 495, 1936.

This is a theoretical presentation of unsubstantiated facts purporting to show why denervation of the kidney causes a drop in blood pressure.

L. N. K.

Lutterloh, Charles H.: The Clinical Significance of the Effects of Posture on Blood-Pressure. The Postural Test as a Means of Classifying Hypotension. *Am. J. M. Sc.* 193: 87, 1937.

There is presented a study of the effects of posture on the blood pressure and pulse rate in normal adults, normal children, and a group of hypotensive individuals as secondary, essential, and primary hypotension.

The response in the normal groups to postural change from the horizontal to the upright position was a slight fall in the systolic blood pressure, a definite rise in the diastolic blood pressure and a rise in the pulse rate. In the secondary and essential hypotension groups a similar response was noted. The primary hypotension group, however, responded abnormally by manifesting a decided fall in both the systolic and diastolic blood pressures with only a slight increase in the pulse rate.

The similarity between primary hypotension and "postural hypotension" is suggested.

A test for circulatory efficiency and vasomotor stability has been outlined, and as a result of this test a classification of hypotension is presented.

AUTHOR.

Brown, J. J. Mason: Intermittent Venous Occlusion in the Treatment of Obliterative Vascular Disease. *Brit. M. J.* 1: 1106, 1937.

Various forms of apparatus for the application of intermittent venous occlusion are described.

Treatment with such apparatus has resulted in the relief of symptoms, healing of ulcerated and gangrenous areas, and increased oseillometric and surface temperature readings.

AUTHOR.

Clara, M.: *Arteriovenous Anastomoses*. München. med. Wehnschr. 83: 651, 1936.

The author summarizes the well-known functions of these important anastomoses. These anastomoses are not only important in regulating blood flow locally but influence as well the rate of flow of the entire body. When they open, the rate is increased; when they close, the rate is decreased. In addition, when these anastomoses open, the venous blood becomes arterialized, a centripetal pulse is transmitted from the arteries to the veins and the temperature of the region is elevated.

L. N. K.

Craig, Winchell McK., and Knepper, Paul A.: *Cervical Rib and the Scalenus Anticus Syndrome*. Ann. Surg. 105: 556, 1937.

The clinical picture of cervical ribs and that of the scalenus anticus syndrome are very similar, as are also the surgical indications and operation. The symptoms result from compression or irritation of the brachial plexus and compression of the subclavian artery. Compression may be due to the presence of cervical rib, an abnormally low position of the shoulder, high fixation of the sternum and ribs, low origin of the brachial plexus, or elevation of the first thoracic rib from spasm of the scalene muscles brought about by irritation of the brachial plexus. When cervical ribs cannot be demonstrated, resection of the scalenus anticus muscle is usually all that is necessary to relieve the symptoms. In the presence of a cervical rib without tendinous attachments and without obvious pressure from behind, resection of the scalenus anticus muscle is all that is necessary, but when there is evident pressure from the cervical rib or its tendinous attachment, resection of the rib and the attachment should be carried out.

In carefully selected cases in which the symptoms point clearly to either cervical rib or the scalenus anticus syndrome, the surgical result is usually excellent. Six cases are presented to illustrate the points in differential diagnosis, surgical indications, and results.

E. A. H.

Beiglböck, W., and Junk, H.: *Muscle Tone and Its Relation to the Peripheral Circulation*. Ztschr. f. klin. Med. 131: 241, 1937.

The method of Henderson, Oughterson, Greenberg, and Searle for measuring intramuscular pressure has been used to study a variety of conditions. The authors agree that the return flow of blood to the heart is in part dependent upon muscle tone, but cite the observation that muscle pressure is not increased in congestive failure with increase in venous pressure as evidence that intra- and extravascular pressures are independent of each other.

The average normal intramuscular pressure in their series of 28 individuals was 76 mm. water. It would have been higher except that several individuals above the age of seventy years were included. All of these had low pressures. They confirm the observations of Henderson, Oughterson, and others, that carbon dioxide and strychnine increase muscular pressure and add that sympathol also does. Histamine decreased it; caffeine, eoramine, and cardiazol had no effect. Operation and most febrile diseases lower it. The most well-marked drops were seen in pneumonia.

J. M. S.

Heckmann, K.: The Significance of the Double Summit in the Waves of the Shadowkymogram. *Klin. Wehnsehr.* 15: 644, 1936.

This double summit in the roentgenkymograph is due occasionally to a cardiac infarct. The author found one instance of right-sided bundle-branch block with this phenomenon. It occurs also in pericardial effusion. It is found without any of these abnormalities and is explained as a systolic displacement of the heart to the left as the aorta lengthens. This causes the second wave, the first being due to systolic contraction.

L. N. K.

Faulkner, James M.: The Treatment of Cardiovascular Emergencies. *New England J. Med.* 216: 747, 1937.

The main body of the paper is concerned with cardiac emergencies, but it ends with a capable reminder about diagnosis and treatment of peripheral vascular collapse or shock. Medically, this condition is frequently unrecognized, yet is as common as cardiac collapse, and demands accurate diagnosis in order that its own peculiar therapy can be applied. The clinical picture is the same as that of surgical shock—prostration, pallor, sweating, pinched features, cold extremities, weak heart sounds, rapid thready pulse, and low blood pressure. There is a disparity between the circulating blood volume and the functioning capacity of the vascular bed. The treatment consists, therefore, in increasing the blood volume or in decreasing the capacity of the vascular bed. The former is the more certain procedure and is effected by the same measures as those used in surgical shock. The latter is effected, to some degree, by the use of central nervous system stimulants: caffeine, strychnine, and various camphor derivatives. Digitalis is of no value, and adrenalin is contra-indicated.

H. M.

Starr, Isaac: Carbaminoylecholine (Doryl or Lentin): Its Action on Normal Persons in Peripheral Vascular Disease, and in Certain Other Clinical Conditions. *Am. J. M. Sc.* 193: 393, 1937.

Carbaminoylecholine chloride is one of the most powerful drugs known. Studies have been conducted on its action after subcutaneous and oral administration to 26 normal volunteers and to a larger number of patients. Special studies of its effect on the heart and circulation have been made in a small group of cases.

The information now at hand concerning its dosage, action, and untoward effects, is sufficient to warrant its cautious use in those cases that its action seems adapted to benefit. The drug causes striking relief of rest pain in certain cases of peripheral vascular disease.

AUTHOR.

Fraenkel, A.: From Empirical to Experimental Digitalis Therapy. *Schweiz. med. Wehnsehr.* 18: 434, 1936.

Intravenous strophanthin is, in the author's opinion, the only method of quantitative digitalis therapy. It permits much better constant control of dosage than digitalis. He believes that this is particularly true in cases with marked cardiac edema. In slight edema he advocates the use of a salt-free diet in addition to intravenous strophanthin. In severe edema salyrgan can be used with the strophanthin.

L. N. K.

# The American Heart Journal

VOL. 14

AUGUST, 1937

No. 2

## Original Communications

### EFFECT ON THE CIRCULATION OF MECHANICAL OCCLUSION OF INDIVIDUAL ARTERIES OF THE EXTREMITIES; RELATION TO ARTERIAL EMBOLISM\*

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IN MANY cases of sudden arterial occlusion resulting from embolism or thrombosis the temperature of the skin of the distal parts of the affected extremity decreases sharply to that of the room or to a temperature approaching that of the room. Gangrene supervenes in about 50 per cent of cases.<sup>1</sup> In sharp contrast to this incidence of gangrene is that following simple ligation. Halsted<sup>2</sup> in 1912 reviewed the reports of ligation of the common iliac artery and found the incidence of gangrene to be about 6 per cent. In 1924<sup>3</sup> he reviewed reports of cases in which the subclavian artery had been ligated and failed to find any evidence that gangrene had been caused by uncomplicated ligation or ligations of either subclavian artery.

Mulvihill, Harvey, and Doroszka<sup>4</sup> reviewed reports of sixty-nine ligations of the common iliac, external iliac, common femoral, and superficial femoral arteries in the period from 1900 to 1930 and found an incidence of gangrene of only 14.7 per cent. In only half of these cases was the gangrene extensive enough to necessitate amputation. Mulvihill and Harvey,<sup>5</sup> in experimental studies on dogs, found that while the incidence of gangrene was small following ligation of the external iliac arteries, the temperatures of the feet were reduced to the level of that of the room in from two to six hours and returned to normal within a variable period of several more hours.

It has been shown that mechanical occlusion of the brachial or femoral artery of human subjects causes a decrease in the temperature of the skin which, however, is not half as fast or as great as if circulation to the arm or leg were arrested by means of a pneumatic cuff. However, it is a common observation in many instances of arterial embolism, which is at least

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†Fellow in Surgery, The Mayo Foundation.



no more than occlusion of an artery, that there is almost immediate cessation of circulation similar to compression of the limb by a pneumatic cuff. Pain occurs in most instances of arterial embolism, yet according to Seifert,<sup>6</sup> ligation of an artery is usually not followed by the type of pain that is observed in arterial embolism.

It was with the hope that some explanation might be found for the comparatively high incidence of gangrene and pain subsequent to arterial embolism, as contrasted with their low incidence following arterial ligation, that this study was undertaken.

#### METHOD OF STUDY

The subjects used in this study had no demonstrable impairment of circulation to the extremities. Studies were conducted with the patients lying in a room, the temperature of which was constant and sufficiently less than that of the limbs so that decreases in the temperature of the limbs could occur. The patients lay in the room for half an hour before the studies were begun to obviate any effects of sudden changes in the temperature of the environmental air and any effect of activity on the temperature of their extremities. Temperatures of the skin of the great toes and of the index fingers were determined in studies on the legs and arms, respectively, by an electric thermometer at the beginning of the test and at five-minute intervals thereafter until ten minutes after pressure on the artery was released. In each test the comparable digit of the opposite extremity was used as a control. Arteries were occluded by a mechanical device that gave a localized area of pressure over the artery to be studied. In all instances except those in which the popliteal and femoral arteries were occluded there was compression of the tissues opposite the rubber pad which occluded the arteries by a metal pad which was a part of the compression device. Absence of the distal pulse was considered indicative of complete occlusion of the artery. This was checked repeatedly to prevent errors arising from slipping of the clamp allowing reestablishment of circulation in the artery.

There was no visible evidence of venous congestion in any of the studies except when the femoral and brachial arteries were occluded. In each test in which the femoral artery was occluded cyanosis and distention of veins were noted. This occurred in only two tests in which the brachial artery was occluded. Obstruction of the veins may have prevented somewhat a decrease in the temperature of the skin in these studies, but this is improbable, as Mulvihill, Harvey, and Doroszka<sup>4</sup> have shown that ligation of the companion vein did not influence a change in temperature resulting from ligation of the external iliac artery of dogs.

In the present studies observations were made following occlusion of the brachial, radial, ulnar, femoral, popliteal, dorsalis pedis, and posterior tibial arteries.

#### RESULTS

*Occlusion of Brachial Artery.*—The brachial artery was occluded above the elbow for thirty minutes in five cases. In none of these cases was there any pain or discomfort except at the site of application of the clamp. In all cases there was a decrease in the temperature of the skin, which varied from 1.5° to 5.0° C. Release of compression caused a rapid increase in the temperature of the skin in only three cases, in two of which the temperature ten minutes after removal of the obstruction exceeded the temperature at the beginning of the test.

The composite graph of these five cases shows a moderate and gradual decrease in temperature while the artery was compressed and evidence of hyperemia after release of the compression (Fig. 1). In two cases the temperature of the control digit diminished in about the same degree as did that of the digit of the extremity of which the artery was occluded; in the remaining three cases there was no significant change in the temperature of the control digit. Study of individual charts used to make this composite graph shows that in all cases except one there was no further decrease in temperature after compression had been maintained for twenty-five minutes, and that in but one case did the temperature of the skin decrease to that of the environmental air, which was  $24^{\circ}\text{C}$ .

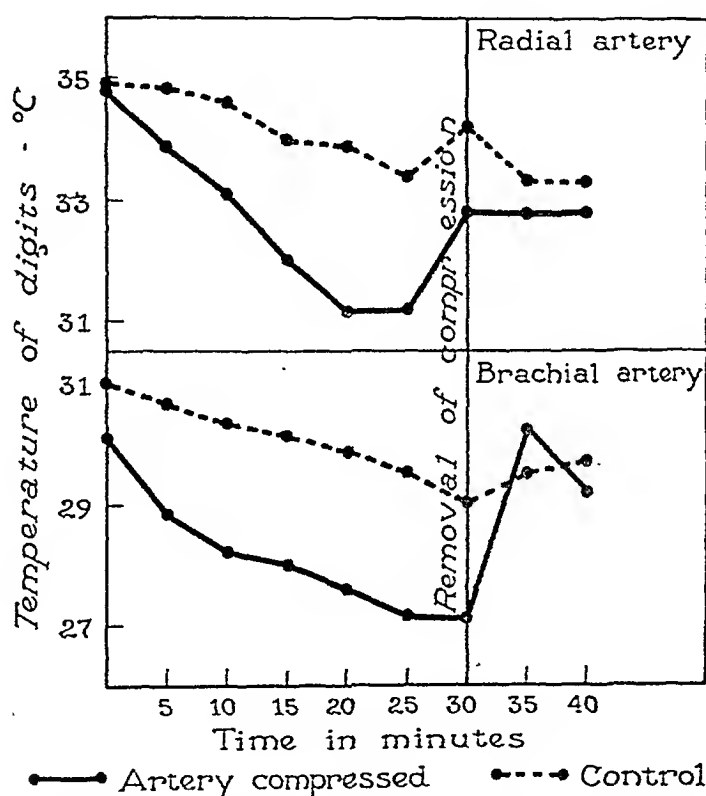


Fig. 1.—Effects produced on temperature of the skin of the digits by occlusion caused by mechanical compression of the radial and brachial arteries.

In the other cases the temperature of the skin did not decrease further, although it was  $2^{\circ}$ ,  $4^{\circ}$ ,  $6^{\circ}$ , and  $8^{\circ}\text{C}$ ., respectively, greater than that of the room.

*Occlusion of Ulnar Artery.*—The ulnar artery was compressed at the wrist in three cases. No significant change in the temperature of the skin of the digit occurred. No unusual symptoms were noted.

*Occlusion of Radial Artery.*—The radial artery was occluded at the wrist in four cases. In no case was there any pain or distress except at the site of compression. The decrease in the temperature of the digit varied from  $2.2^{\circ}\text{C}$ . to  $7.0^{\circ}\text{C}$ . In three cases the temperature increased again in spite of maintained compression of the artery at periods varying

from fifteen to twenty-five minutes after compression was begun. In no case was the minimal temperature of the digit as low as that of the room; it failed by  $2.0^{\circ}\text{C}$ .,  $4.4^{\circ}\text{C}$ .,  $2.2^{\circ}\text{C}$ ., and  $9.0^{\circ}\text{C}$ ., respectively, to diminish to that of the room. In three cases the temperature of the control digit decreased somewhat less than that of the digit of the limb whose artery was compressed, and in one case it actually increased. The composite graph of these four cases indicates a gradual decrease of temperature until twenty minutes after the application of compression, then an increase in temperature which was quite marked before compression was removed (Fig. 1).

*Occlusion of Femoral Artery.*—The femoral artery was compressed just below the inguinal ligament in five cases. In all cases there was a moderate decrease in temperature which varied from  $4^{\circ}\text{C}$ . to  $1^{\circ}\text{C}$ . Venous congestion of the limb was marked in all cases, apparently because of occlusion of the accompanying femoral vein. This venous congestion caused a feeling of fullness in the limb within ten to fifteen minutes after compression, and in three cases this became so uncomfortable in twenty to twenty-five minutes that the test had to be discontinued. Subsequent to release of the compression there was a prompt increase in the temperature of the skin in three cases. The graph (Fig. 2) represents the results of study of these five cases for the first twenty minutes, of four cases for twenty-five minutes, and of two cases for thirty minutes. That part of the graph indicating determination of the temperature of the skin following removal of compression is a composite of the results in all five cases. The temperature of the skin failed to decrease to that of the room by  $3.0^{\circ}\text{C}$ .,  $2.1^{\circ}\text{C}$ .,  $1.6^{\circ}\text{C}$ ., and  $0.4^{\circ}\text{C}$ ., respectively, in four cases; in one case the temperature decreased to that of the room, which was  $26.5^{\circ}\text{C}$ . It should be emphasized, however, that the temperatures were still decreasing in all instances when the tests were terminated.

*Occlusion of Popliteal Artery.*—The popliteal artery was occluded in the popliteal space in three cases, and in all cases there was a prompt drop in peripheral skin temperatures (Fig. 2). Numbness began to develop in from fifteen to twenty minutes, and soon the patient stated that the distal part of the limb felt as though it were dead. This may have been due to compression of the peroneal nerve. Release of the obstruction caused a prompt increase in temperature in all but one case. In an additional test not included in Fig. 2 the subject slept. As a result, the temperature of the control digit increased  $6^{\circ}\text{C}$ ., but that of the digit of the limb in which the popliteal artery was occluded remained stationary. Although the minimal temperature resulting from obstruction of the popliteal artery was not as low as that of the room by  $5.2^{\circ}\text{C}$ .,  $2.0^{\circ}\text{C}$ ., and  $1.5^{\circ}\text{C}$ ., respectively, it should be emphasized that it was still decreasing when the tests were terminated.

*Occlusion of Posterior Tibial Artery.*—The posterior tibial artery was occluded at the ankle in five cases. In two of the cases there was no

change in the temperature of the skin. In the three remaining cases the temperature diminished from  $1.5^{\circ}\text{C}.$  in one case to  $4.0^{\circ}\text{C}.$  in another. In all instances the decline in temperature had stopped before the compression was removed. The composite graph of these five cases indicates a gradual but small decrease in the temperature and an increase following removal of compression (Fig. 2). The minimal temperatures resulting from occlusion of the artery failed to reach that of the room by

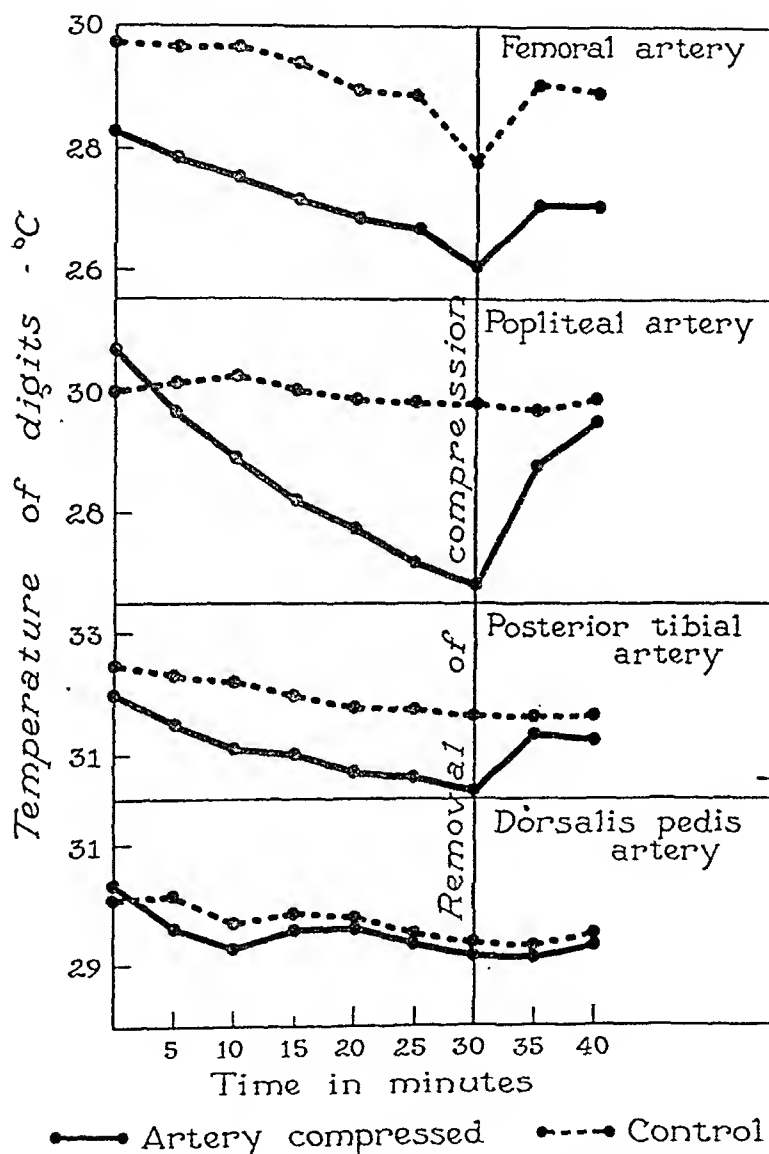


Fig. 2.—Effects on temperature of the skin of the digits produced by occlusion caused by mechanical compression of the femoral, popliteal, posterior tibial, and dorsalis pedis arteries.

$3.0^{\circ}\text{C}.$ ,  $0.7^{\circ}\text{C}.$ , and  $2.6^{\circ}\text{C}.$ , respectively, in the three cases in which the temperature was influenced by the procedure.

*Occlusion of Dorsalis Pedis Artery.*—The dorsalis pedis artery was occluded over the dorsum of the foot in five cases. In four cases there was a decrease in temperature varying from  $1.4^{\circ}\text{C}.$  in one case to  $4.0^{\circ}\text{C}.$  in another. In two of these cases there was an increase in temperature before compression was removed, which was temporary in one case but

which persisted in another case until the obstruction was removed. In the fifth case there was actually an increase in the temperature while compression was applied. The composite graph of these tests shows a minimal decrease in the temperature but is slightly misleading since it includes the results of study of the case in which there was actually a rise in temperature (Fig. 2).

#### SUMMARY OF RESULTS

These studies indicate that mechanical occlusion of identical arteries of different individuals produces varying results on the circulation. This seems attributable to the variability of function of identical arteries of different individuals. Compression of the ulnar artery produced no effect on circulation to the index finger as determined by calculation of the temperature of the skin. Compression of the dorsalis pedis and posterior tibial arteries individually caused reduction of the circulation in only a minor degree. These arteries individually appear, therefore, to be of minimal importance in maintaining circulation to the acral parts. Mechanical compression of the brachial artery caused reduction of the temperature of the skin to an average of  $27.0^{\circ}$  C. in an environmental temperature considerably lower than this in about twenty-five minutes, following which there was ordinarily no further reduction in temperature. Compression of the radial artery caused a reduction of the temperature of the skin to an average of about  $31.0^{\circ}$  C. in about twenty minutes, following which there was ordinarily no further reduction. The arteries of the upper extremity, in order of their importance in maintaining circulation, are therefore the brachial, radial, and ulnar. Compression of the femoral artery caused a decrease of the temperature of the skin of the great toe to an average of  $26.0^{\circ}$  C. and that of the popliteal to an average of about  $27^{\circ}$  C. In both instances the temperature of the toes was still decreasing at the end of thirty minutes of compression. In the lower extremity, therefore, the femoral artery appears somewhat more important than the popliteal artery in maintaining circulation to the foot, while the dorsalis pedis and posterior tibial arteries individually are of very minor importance.

#### COMMENT

These studies appear to have considerable importance in understanding some of the events in arterial embolism. It appears from our studies that occlusion by mechanical compression of the main arteries of the extremities for periods until there is no further diminution in circulation as a result of the compression does not produce pain except the distress produced by pressure at the site of occlusion and except occlusion of the femoral and popliteal arteries in which studies distress seemed to be produced by venous occlusion and pressure on the peroneal nerve respectively. In no instance was there simulation of severe pain ob-

served in embolism. This is strange since occlusion of these arteries by an embolus is frequently attended by much pain. Apparently, however, as Lewis<sup>7</sup> has pointed out, the pain of arterial embolism does not occur coincidentally to lodgment of the embolus but results from ischemia produced by embolism. This contention is supported by our observations as mechanical occlusion, which produces the same effect on an artery, so far as circulation through it is concerned as embolism does, does not produce pain simulating that due to embolism. In this connection it is of some interest to note that slow occlusion of arteries, such as that which occurs in thromboangiitis obliterans or arteriosclerosis obliterans, does not produce pain ordinarily, being comparable in this regard to arterial compression. It is quite apparent, therefore, that pain in arterial embolism is not due to mere mechanical obstruction of the artery by the embolus. If it were true that embolism were nothing more than arterial occlusion, it would be uniformly painless, as is compression of an artery.

In a similar manner our studies indicate that the diminution of circulation in arterial embolism is not due entirely to mere mechanical obstruction of an artery, since the effects of embolism on the circulation frequently exceed greatly those of simple obstruction of an artery or ligation of it.<sup>1-4</sup> If this were not true, embolic obstruction of the dorsalis pedis, posterior tibial, or ulnar arteries would produce no grossly detectable effect on circulation. Also, embolic occlusion of the brachial and radial arteries would produce only minor impairment of the circulation.

There appears to be an additional factor in arterial embolism which accounts for pain and the diminution of circulation which is absent following simple ligation or compression of an artery. This seems to be diffuse arterial spasm.\* Arterial spasm in embolism is known to exist, for it has actually been seen by Seifert,<sup>6</sup> by Gosset, Bertrand, and Patel<sup>8</sup> and by others. Its presence has been demonstrated indirectly by observations that papaverine hydrochloride, which is a vasodilator, may cause remarkable reestablishment of circulation within a short period after embolism.<sup>6, 9</sup> Good results have also been reported by Herrmann and Reid<sup>10</sup> following use of intermittent suction and pressure, which effects vasodilation. Also, the circulation of many extremities, which is greatly reduced shortly after embolism, may spontaneously return to a nearly normal level. In all cases of embolism in which there is recovery of circulation after an original marked decrease in it, the embolus, that is, arterial occlusion, has remained unchanged yet circulation improves and pain disappears. It is customary to attribute this to increased circulation through collateral arteries not influenced primarily by embolism. However, in view of our present studies on arterial compression it ap-

\*If Lewis' contentions are correct, arterial spasm only causes pain indirectly by producing ischemia.

pears that these arteries are abnormally spastic as a result of embolism, since were this not true marked diminution in circulation would be absent in cases of peripheral arterial embolism. The variation in pain and circulatory disturbances resulting from roughly similar instances of embolism and the variability of recovery are, in all probability, manifestations of the degree and persistence of spasm in arteries not directly occluded by emboli as well as of the importance to circulation of the artery occluded.

#### CONCLUSIONS

Simple arterial compression produces effects dissimilar to those of arterial embolism in that pain observed in embolism is absent and the effect of such compression on circulation is usually not great. This dissimilarity appears to be attributable to arterial spasm in embolism and its absence in simple arterial compression.

#### REFERENCES

1. McKeehnle, R. E., and Allen, E. V.: Sudden Occlusion of the Arteries of the Extremities; Study of 100 Cases of Embolism and Thrombosis, *Surg., Gynec. & Obst.* 63: 231, 1936.
2. Halsted, W. S.: The Effect of Ligation of the Common Iliac Artery on the Circulation and Function of the Lower Extremity. Report of a Cure of Iliofemoral Aneurism by the Application of an Aluminum Band to That Vessel, *Bull. Johns Hopkins Hosp.* 23: 191, 1912.
3. Halsted, W. S.: Ligations of the Left Subclavian Artery in Its First Portion, *Johns Hopkins Hosp. Rep.* 21: 1, 1920-1924.
4. Mulvihill, D. A., Harvey, S. C., and Doroszka, V.: Simultaneous Ligation of Vein in Ligation of Large Arteries; Experimental Study, *Am. J. Surg.* 13: 431, 1931.
5. Mulvihill, D. A., and Harvey, S. C.: Studies on Collateral Circulation: Thermic Changes After Arterial Ligation and Ganglionectomy, *J. Clin. Investigation* 10: 423, 1931.
6. Seifert, E.: Die Deutung des Schmerzes bei der arteriellen Embolie, *Deutsche Ztschr. f. Chir.* 232: 187, 1931.
7. Lewis, Thomas: Pain as an Early Symptom of Arterial Embolism and Its Causation, *Clin. Sc.* 2: 237, 1936.
8. Gosset, A., Bertrand, Ivan, and Patel, Jean: Sur la physio-pathologie des embolies artérielles des membres (recherches expérimentales), *Ann. d'anat. path.* 9: 841, 1932.
9. Allen, E. V., and MacLean, A. R.: Treatment of Sudden Arterial Occlusion With Papaverine Hydrochloride; Report of a Case, *Proc. Staff Meet., Mayo Clin.* 10: 216, 1935.
10. Herrmann, L. G., and Reid, M. R.: Passive Vascular Exercises; Treatment of Peripheral Obliterative Arterial Diseases by Rhythmic Alteration of Environmental Pressure, *Arch. Surg.* 29: 697, 1934.

## AN APPROACH TO THE DIAGNOSIS OF CONGENITAL HEART DISEASE\*

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THE attitude toward congenital heart disease is changing. It is becoming more generally recognized that in a goodly number of cases the correct approach will lead to a correct anatomical diagnosis clinically. Because of the prominence of the physical signs, congenital cardiac anomalies seldom escape detection for long, but too often an erroneous prognostic significance is attached to these signs. Frequently enough to demand attention, an individual with a congenital cardiac anomaly dies at an advanced age from causes perhaps unrelated to the murmur for which his activities had been restricted since childhood. Then there is the other side of the picture, represented by the sudden death of an individual who had been in apparently robust health, as a result of paradoxical embolism, or again, by the development of subacute bacterial endocarditis in an individual whose bicuspid pulmonic valve had hitherto not given rise to a single sign or symptom. Quite a proportion of congenital cardiac defects are, of course, of such a nature as to be either entirely incompatible with life or permit only a short and crippled existence.

It therefore becomes increasingly interesting, and in view of the wide differences in prognosis with regard to various congenital lesions, very important to differentiate them, not only from one another, but also from acquired cardiac disease. What, then, is the approach to the clinical recognition of these entities? Their clinical recognition depends on: (1) an understanding of the ontogenesis of each of these anomalies, (2) an understanding of the physiological alterations imposed on the cardiovascular system by their presence, and (3) the correct interpretation of groups of findings which form in many cases a syndrome characteristic, or at least extremely suggestive, of a particular anomalous arrangement.

### THE GENESIS OF CARDIOVASCULAR ANOMALIES

If one begins with the premise that the cardiovascular system recapitulates its ancestral history during the course of its own development, it is reasonable to expect that, if arrest of development does occur, it will represent the adult form of one of the lower vertebrate series, dependent on the stage at which arrest takes place. The intermediate stages are, in fact, particularly well illustrated in the develop-

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\*From the Section on Cardiology, The Mayo Clinic.



ing mammalian heart because it assumes functional activity at a very early stage of gestation. As in its phylogenetic history, it starts as a simple tubelike structure with the same subdivisions as the adult fish heart (Fig. 1, *a*). Expressed in the simplest form its development from then on consists essentially in: (1) septal formations dividing the auricle, the ventricle, the bulbus cordis, and the common aorta or truncus arteriosus each into two sections (Fig. 1, *b*); (2) torsion of the cardiac tube; (3) development of the bulbus cordis; (4) the incorporation of the sinus venosus into the right auricle (Fig. 1, *b*); (5) the evolution of the aortic arches, some being obliterated, others becoming the permanent aortic arch, pulmonary artery and their branches, and (6) closure of fetal channels after birth.

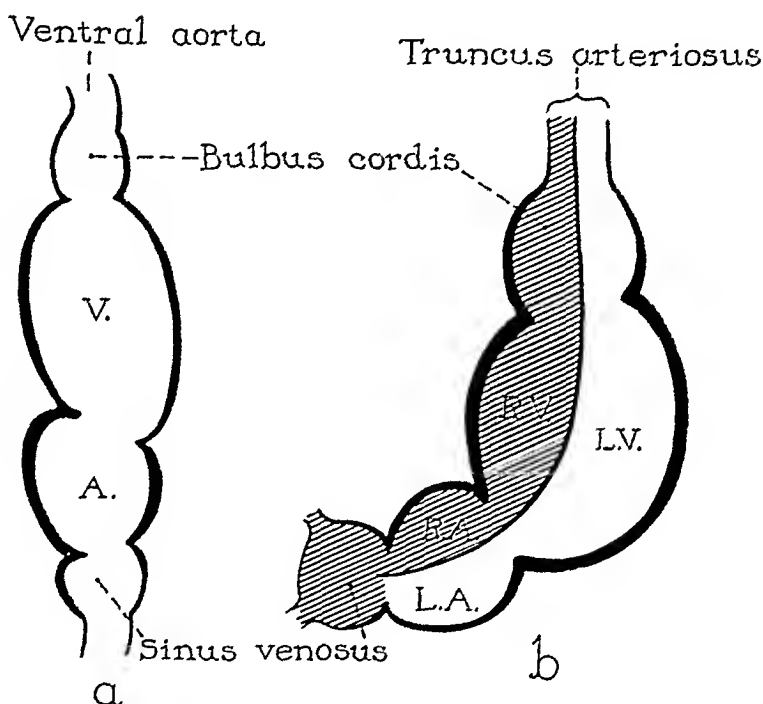


Fig. 1*a*.—Fish type of heart, which is similar to the heart in the fourth-week human embryo; *b*, septal formation; The sinus venosus is incorporated in the right auricle, the bulbus cordis becomes part of the right ventricle (mainly) and of the left ventricle, and a clockwise rotation occurs in the bulboventricular part of the cardiac tube.

*Septal Formations.*—This process is the physiological response on the part of the cardiac tube to the evolution of a lung-respiratory system so that the venous and arterial systems eventually become completely separated from one another. Any of these septal formations may be incomplete, resulting in any one of a variety of well-known defects (Table I). The *cor biloculare* in which no septa have developed is the replica of the fish heart. The amphibian form is represented by the *cor triloculare biatriatum* in which the interventricular septum is absent. Small interventricular septal defects, such as the *maladie de Roger*, resemble the adult form of the heart of some of the higher reptiles.

Now if it is realized that the different developmental processes which are being described are occurring more or less synchronously, it is apparent that multiple sites are liable to be involved, though isolated anomalies, of course, frequently occur. Normally, septal formations are complete after the seventh week of fetal life.

*Torsion of the Cardiac Tube.*—At an early stage the cardiac tube becomes kinked on itself by virtue of the fact that its extremities are relatively fixed as the primitive heart elongates (Fig. 1, *b*). The torsion to which I refer, however, applies to a clockwise rotation of the

TABLE I  
CLASSIFICATION OF CONGENITAL HEART DISEASE

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I. Anomalies associated with septal formation:
1. Cor biloculare
2. Cor triloculare biatriatum
3. Cor triloculare biventriculare
4. Auricular septal defects
5. Ventricular septal defects
6. Persistent truncus arteriosus
II. Anomalies associated with torsion of the cardiac tube and
III. Anomalies associated with development of the bulbus cordis:
1. Subaortic stenosis
2. Pulmonary stenosis
3. Transposition of great vessels
4. Tetralogy of Fallot
5. Eisenmenger's complex
6. Anomalies of the aortic and pulmonic valve cusps
IV. Anomalies associated with development of the aortic arches:
1. Persistent right aortic arch with isthmus stenosis of the left arch
2. Double aortic arches
3. Coarctation of the aorta
4. Anomalous origin of vessels arising from the aortic arch
5. Patent ductus botalli
V. Dextrocardia
VI. Anomalies of the coronary vessels

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bulboventricular end of the cardiac tube during which the aorta moves toward the left and partially behind the commencement of the pulmonary artery. If one will examine the anterior aspect of the adult normal heart this relationship will become clear. This torsion is necessary in order to bring the left ventricle into juxtaposition with that part of the truncus arteriosus which is destined to become the aorta, and the right ventricle into juxtaposition with the pulmonary artery. As in the adult heart of certain reptiles, there is a transitory stage in the human heart in which there are two aortae connected with the left ventricle, each with two cusps. In the process of torsion, the right aorta is obliterated whereas the left remains open to become the out-flow chamber of the left ventricle. If this process of torsion is arrested, the aorta is left in a dextroposed position, in which case the right aorta persists instead of the left, or the right and left aortae may fuse

to form a large aortic trunk. In either case this dextroposed aorta, instead of bearing the normal relationship to the left ventricle, overrides the interventricular septum (which is usually incomplete) and the right ventricle (Fig. 2). In other words, the great vessels (the aorta and pulmonary artery) are transposed, and this transposition may be present in varying degrees depending on the degree of torsion that has occurred. Sometimes there is a small niche in the right ventricle which represents the obliterated right aorta. It is extremely likely that other developmental defects will accompany such a gross deviation from the normal, such as imperfect septal formations and incomplete evolution of the bulbus cordis.

Here, then, one sees the genesis of one of the important and interesting anomalies representing arrest at the reptilian stage, namely, the tetralogy of Fallot. This consists of dextroposition of the aorta, with an interventricular septal defect, pulmonary stenosis, and an hyper-

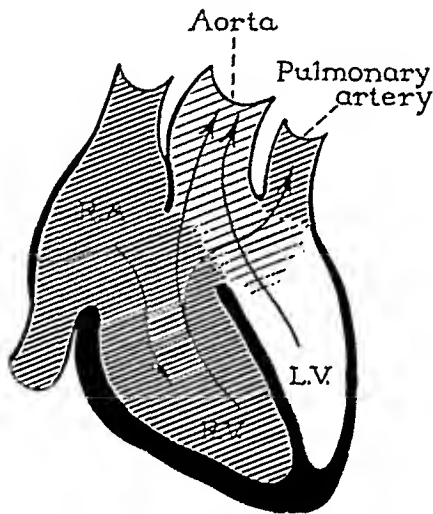


Fig. 2.—The tetralogy of Fallot, showing a large aorta which is dextroposed and overrides the interventricular septum. The latter is incomplete. The pulmonary artery is stenosed and the right ventricle is hypertrophied. The left auricle is not indicated in this diagram.

trophied right ventricle. Cusp anomalies are frequently associated with the tetralogy, especially in the form of bicuspid leaflets which are, interestingly enough, the normal for the reptilian species.

*The Development of the Bulbus Cordis.*—Essentially this consists of the incorporation of the major portion of the bulbus into the right ventricle, to form the conus arteriosus, and a smaller portion into the left ventricle. If this process is incomplete, the corresponding ventricle will be constricted or stenosed in that region. Thus in the case of the left ventricle there will be a stenotic band below the aortic valve, that is, a subaortic stenosis. Its counterpart in the right ventricle consists of a subpulmonic or infundibular stenosis.

In the genesis of some of the stenotic congenital lesions, fetal inflammatory processes probably play a part.

*The Incorporation of the Sinus Venosus into the Right Auricle.*—In the adult heart the sinus venosus is represented by that part of the right auricle which receives the blood from the superior and inferior venae cavae anatomically known as the sinus venarum.

*The Development of the Aortic Arches.*—Briefly stated, there are six pairs of aortic arches connecting the primitive ascending aorta to the primitive descending aorta. They are not all present at the same time. The left fourth arch becomes the aortic arch. The right fourth arch forms the innominate artery and the beginning of the right subclavian artery. The sixth arch gives origin to the pulmonary artery, and on the left side, to the ductus botalli.

The chief anomalous developments met are persistence of both fourth arches and persistence of the right arch in place of the left. The latter arrangement is closely related to coarctation of the aorta. The very

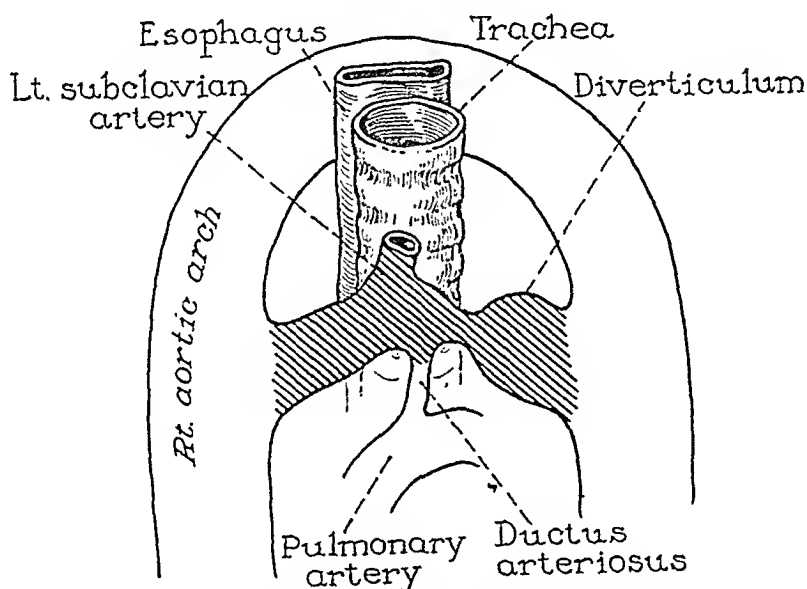


Fig. 3.—Persistent right aortic arch, representing the right fourth aortic arch. Note its relation to the trachea and esophagus. The shaded part represents the left fourth arch which normally becomes the aortic arch.

plausible explanation has been given that if for any reason the left fourth arch becomes stenosed, then one of two terminations results, namely, coarctation, or the right fourth arch may remain patent, forming the aortic arch.<sup>1</sup> In the latter instance the patency of the right arch is salutary; it usually runs over the right bronchus and behind the trachea and esophagus to join the descending aorta. The left arch is here represented by the left subclavian artery, the stenosed fourth arch and a diverticulum which would have formed that part of the aortic arch between the point where the ductus botalli joins it and the descending aorta if the left arch had been normally patent (Fig. 3). Coarctation of the aorta is frequently associated with aneurysms of the circle of Willis.<sup>2, 3</sup> Permanent patency of the ductus arteriosus (botalli) should be considered together with anomalies of the aortic arches, as the former is derived embryologically from the latter. The

opening up of the pulmonary circulation after birth usually leads to gradual closure of the ductus. Should conditions remain such that pressure in the pulmonary circuit and the aortic arch remains the same as before birth, the duct will remain patent. Patency of the ductus is frequently associated with other anomalies of the aortic arches.

*Closure of Fetal Channels.*—This refers to the closure of the ductus arteriosus and the foramen ovale.

*Classification.*—Associated with each of these processes, anomalous developments may occur and congenital cardiac lesions conveniently classify themselves under the corresponding subdivisions shown in Table I. Such a classification is self-explanatory and easily remembered. Viewed in this light, the corresponding physiological disturbance caused by each anomalous condition is readily understood and the symptoms and physical findings are more readily explained. There is, therefore, no particular advantage in dividing them into clinical groups.

#### CERTAIN FACTS AND FINDINGS WHICH SHOULD LEAD ONE TO SUSPECT THE PRESENCE OF A CONGENITAL CARDIAC ANOMALY

*Bruits Not Explainable on the Basis of the Conventional Acquired Valvular Lesions.*—These have usually been noted in infancy and are rather constant over a period of years. The point of maximal intensity should be noted as well as the direction in which the murmurs are propagated.

*Thrills.*—These are frequently present over the areas of maximal intensity of the bruits, and both bruits and thrills become more readily elicited clinically after exercise.

*Evidence of Venous-Arterial Shunt, With the Usual Manifestations: Cyanosis, Polycythemia, and Clubbed Fingers and Toes.*—The group of cases in which the venous-arterial shunt is transitory, depending on temporarily induced increased pressure on the venous side, frequently have a history of episodes of dyspnea or cyanosis. A rather unique feature relative to the cyanosis of congenital heart disease is the absence of edema when the cyanosis is quite pronounced.

*Any Unusual Heart Contour in the Roentgenogram, Such as a Prominent Pulmonary Artery.*—Points readily overlooked are: lack of prominence of the aortic knob; shadows to the right of the sternum running up toward the right sternoclavicular joint, as is seen in persistent right aortic arch, and erosion of ribs, which may in itself be diagnostic of coarctation of the aorta. These features are often better elicited by fluoroscopy.

*Hypertension.*—In a young individual hypertension should lead one to examine the strength of the pulsation in the abdominal aorta and femoral arteries and to look for other evidence to exclude or confirm the presence of coarctation of the aorta.

*Congenital Anomalies.*—Congenital anomalies in any part of the body should lead one to examine carefully for cardiac anomalies. In Ab-

bott's series,<sup>4</sup> 18.8 per cent of patients had anomalies elsewhere. Mongolian idiots, too, are prone to have congenital cardiac lesions.

*Subacute Bacterial Endocarditis.*—This frequently occurs as a complication of congenital heart disease.

*Comment.*—Once an anatomical diagnosis has been arrived at, the resultant physiological disturbance should be reasoned out and examination should be made to see if the physical findings fit the case. There will in many instances be room for differences of opinion in the interpretation of physical signs, but it is only by making a concerted effort to establish a detailed diagnosis in each instance that one is going to become more expert in recognizing them.

#### THE ELECTROCARDIOGRAM IN CONGENITAL HEART DISEASE

If one can divorce from one's mind the idea that congenital heart disease is an entity separate from heart disease in general and adheres to the physical principles governing electrocardiography, the subject becomes much more clearly understood. With the single exception of dextrocardia with complete situs transversus, there are no diagnostic electrocardiographic patterns in congenital anomalies. The information so obtained serves merely as one link in the chain of evidence.

Again I must refer to the physiological alterations concerned in any particular anomaly. If the condition is such as to throw added strain on the left ventricle, as in coarctation of the aorta or subaortic stenosis, a left axis deviation in the electrocardiogram will reflect such a condition as eloquently as it does in arterial hypertension or in acquired aortic disease. If myocardial changes result as a consequence, T-wave changes in Leads I and II can be expected to follow.<sup>5</sup> It so happens that the majority of congenital defects are attended sooner or later by strain on the right side of the heart, either because of arteriovenous shunts or stenotic pulmonary effects. Corresponding roughly to the degree, there will be right axis deviation and perhaps T-wave alterations in Leads II and III.<sup>5</sup> P-waves may be exaggerated, as in acquired mitral stenosis, indicating greater auricular activity.

Conduction interferences are at times of considerable diagnostic help when caused by interventricular septal defects, while coronary types of T-wave changes have been noted when the coronary vessels originated from the pulmonary artery.<sup>6</sup>

Auricular fibrillation is very unusual except in a widely patent foramen ovale accompanied by distention of the right auricle.

Very meager information is forthcoming from the literature regarding the fourth lead in cases of congenital heart disease. In the past year a clinical diagnosis of congenital heart disease was made in forty-three cases. A fourth lead (Wolferth) was recorded in seventeen cases. The frequency of abnormal changes is indicated in Table II. It is apparent again that such changes are not in any sense diagnostic but

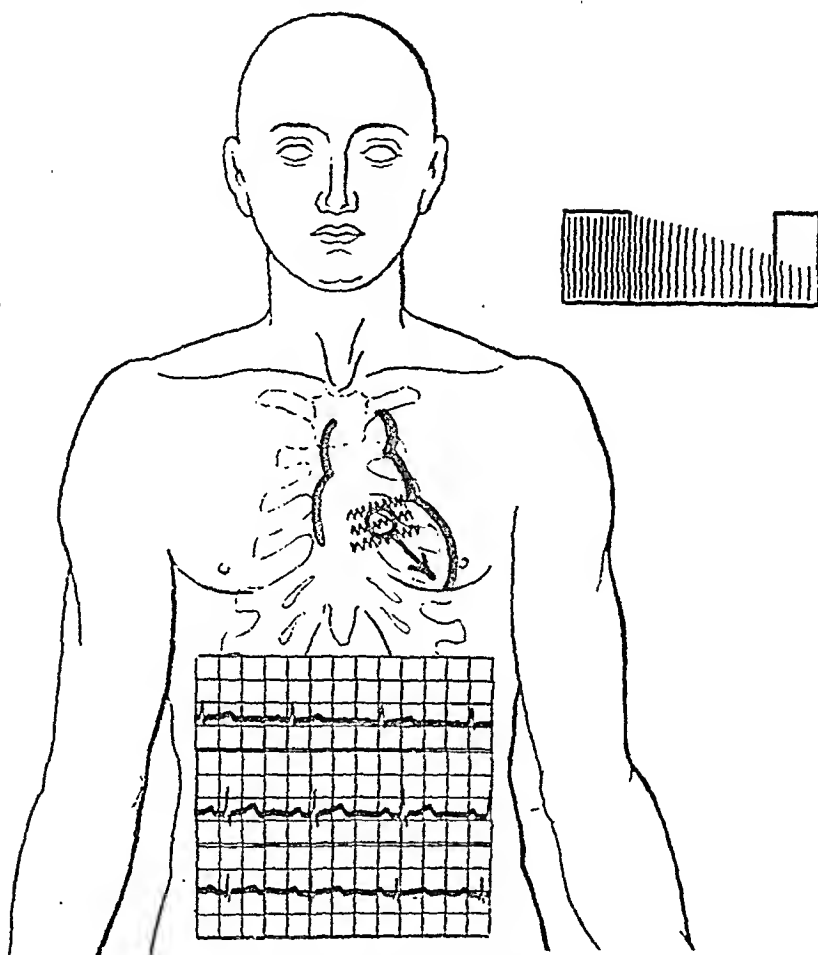
TABLE II  
A RECORD OF FOURTH LEADS IN CASES OF CONGENITAL HEART DISEASE

CASE	AGE, YR.	CLINICAL DIAGNOSIS	AXIS DEVIATION	FOURTH LEAD (WOLFEARTH)	CARDIAC SYMPTOMS	COMMENT
1	227	Auricular septal defect and mitral stenosis	Marked R. V. P.*	Upright T-wave Absent R-wave	Early decompensation with cyanosis and clubbing	Exaggerated P <sub>2</sub> and P <sub>3</sub> waves
2	45	Patent ductus arteriosus and patent interventricular septum	R. V. P. (despite the presence of a superimposed hypertension)	Diphasic T-wave Absent Q-wave	Decompensation	Exaggerated P <sub>2</sub> and P <sub>3</sub> ; diphasic T <sub>2</sub> and T <sub>3</sub> ; delayed A-V conduction
3	22	Auricular septal defect and patent ductus arteriosus	Marked R. V. P.	Upright T-wave	Early decompensation	Exaggerated P <sub>2</sub> and P <sub>3</sub>
4	41	Patent ductus arteriosus with mitral and aortic endocarditis	R. V. P.	Upright T-wave with elevated R-T segment	Early decompensation	Auricular fibrillation
5	27	Patent ductus arteriosus	R. V. P.	Diphasic T-wave	Absent	
6	37	Patent ductus arteriosus	R. V. P.	Normal	Absent	
7	16	Ventricular septal defect	No preponderance	Normal	Absent	
8	61	Patent ductus arteriosus	R. V. P.	Normal	Absent	
9	45?	Ventricular septal defect	No preponderance	Normal	Absent	
10	23	Patent ductus arteriosus	No preponderance	Normal	Absent	
11	25	Ventricular septal defect	No preponderance	Normal	Absent	
12	52	Auricular septal defect with mitral stenosis	R. V. P.	Isoelectric T-wave	Decompensation	Auricular fibrillation
13	24	Patent ductus arteriosus	R. V. P.	Normal	Absent	
14	20	Ventricular septal defect with patent ductus arteriosus	R. V. P.	Large inverted T-wave	Poor cardiac reserve	Inverted T <sub>2</sub> and T <sub>3</sub> ; incomplete bundle-branch block; auricular fibrillation
15	19	Patent ductus arteriosus with ventricular septal defect	R. V. P.	Slight depression of R-T segment	Dyspnea on exertion	
16	27	Patent ductus arteriosus	No preponderance	Normal	Absent	
17	19	Ventricular septal defect and probable patulous foramen ovale	Marked R. V. P.	Deeply inverted T-wave, "M", notching of QRS with diminished Q and exaggerated S-wave	Dyspnea on exertion, Cyanosis and clubbing present	Exaggerated P <sub>2</sub> , Incomplete bundle-branch block, Inverted T <sub>2</sub> and T <sub>3</sub> .

\*Right ventricular preponderance.

seem to be associated with a cardiac mechanism which throws an added strain on the right side of the heart, particularly if the strain is pronounced or of long standing.

A group of twenty-six cases reported by Edeiken, Wolferth, and Wood,<sup>7</sup> in which the fourth lead showed the only electrocardiographic abnormality, included one congenital anomaly. The fourth lead was upright in this case and it was associated with right ventricular preponderance to the extent of  $+128^{\circ}$ .



○ point of maximal intensity of bruit  
 → main direction in which propagated  
 ~~~~~ location of thrill, if present  
 □ musical characteristics of bruit

Fig. 4.—Interventricular septal defect; the heart contour is normal and the electrocardiogram is normal.

#### THE DIAGNOSTIC FEATURES OF INDIVIDUAL CONGENITAL ANOMALIES

*Interventricular Septal Defect (Maladie de Roger).*—Mechanism. There is an arteriovenous shunt because of the higher pressure in the left ventricle. With a failing left ventricle, or with increased pressure on the right side of the heart, the flow is reversed and under these conditions only does cyanosis occur.

The syndrome (Fig 4). The bruit and the thrill are the important findings. Roger's original description<sup>8</sup> of the bruit was as follows:



"This murmur is uncomplicated by other murmurs; it begins with systole and is prolonged to such an extent that it entirely covers the natural tic-tac of the normal heart sounds." The heart's shape is usually normal, as is the electrocardiogram. Occasionally, however, there is evidence of interference with the conductive system. Symptoms are absent, but subacute bacterial endocarditis is a frequent complication.

*Interauricular Septal Defect (Widely Patent Foramen Ovale).*—Mechanism. The shunt again is arteriovenous until conditions arise which cause a reversal of pressures. Cyanosis is thus a frequent terminal event.

The syndrome. Until such events as just described occur, there are generally no signs or symptoms, no cardiac enlargement or abnormal contour features, and the condition may thus remain unsuspected and undiagnosed. A patent foramen ovale should be suspected when (1) there is a history of cyanotic spells or undue cyanosis during pulmonary infections, and (2) when systolic or presystolic bruits, with or

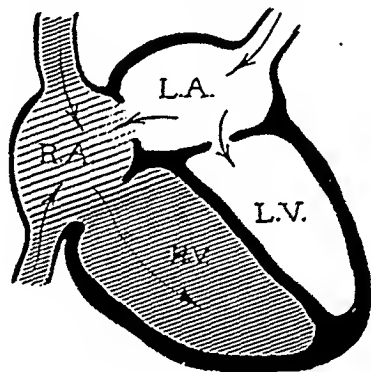


Fig. 5.—Lutembacher's disease (patulous foramen ovale with mitral stenosis).

without thrills, are audible over the upper portion of the sternum and are not otherwise explainable. When symptoms do occur, there is usually evidence of right ventricular hypertrophy with enlargement of the pulmonary artery and also of the right auricle. The roentgenologic and electrocardiographic findings will then be in keeping with such events.

Comment. Among congenital heart lesions, a widely patent foramen ovale is the only one which at times terminates in auricular fibrillation. Paradoxical embolism may occur, but subacute bacterial endocarditis is a rare complication.

*Lutembacher's Disease (Mitral Stenosis and Interauricular Septal Defect).*—Mechanism. Something of a vicious circle is created by the fact that an easier egress exists through the interauricular septal defect for the blood in the left auricle than through the stenosed mitral orifice (Fig. 5). This means that blood already aerated reaches the right side of the heart, to be sent to the lungs again. While this is no special disadvantage at first, the right ventricle soon hypertrophies,

and when it fails, as it inevitably does, a reversal of blood eventually results from the right side of the heart to the left, and cyanosis develops. As decompensation is controlled the degree of cyanosis decreases.

The syndrome. The syndrome consists of: (1) the auscultatory findings of mitral stenosis at the apex, (2) at times, a high-pitched bruit audible over the upper portion of the sternum accompanied by a thrill (in a recent case the correct diagnosis was arrived at by this finding),



Fig. 6.—Roentgenologic appearance of Lutembacher's disease, showing the enormous dilatation of the pulmonary vessels (simulating a mediastinal tumor) and the rounded apex, representing a much hypertrophied right ventricle.

(3) roentgenologic evidence of cardiac hypertrophy, especially affecting the right ventricle, a prominent pulmonary conus and an enlarged right auricle; the aortic knob is smaller than normal, and the pulmonary vessels may be so increased in prominence as to simulate pathologic mediastinal lymph nodes (Fig. 6) (in the case just referred to the preliminary diagnosis was mitral stenosis and Hodgkin's disease), and (4) marked right axis deviation in the electrocardiogram.

Comment. Right heart failure eventually results.

*Subaortic Stenosis.*—Mechanism. The mechanism is the same as in acquired aortic stenosis.

The syndrome. The syndrome consists of: (1) a harsh systolic bruit at the base transmitted to the vessels in the neck, (2) an accompanying thrill, (3) forceful action of the left ventricle in contrast to a weak radial pulse, (4) absence of symptoms, and (5) evidence of left ventricular strain roentgenologically as well as electrocardiographically (Fig. 7).

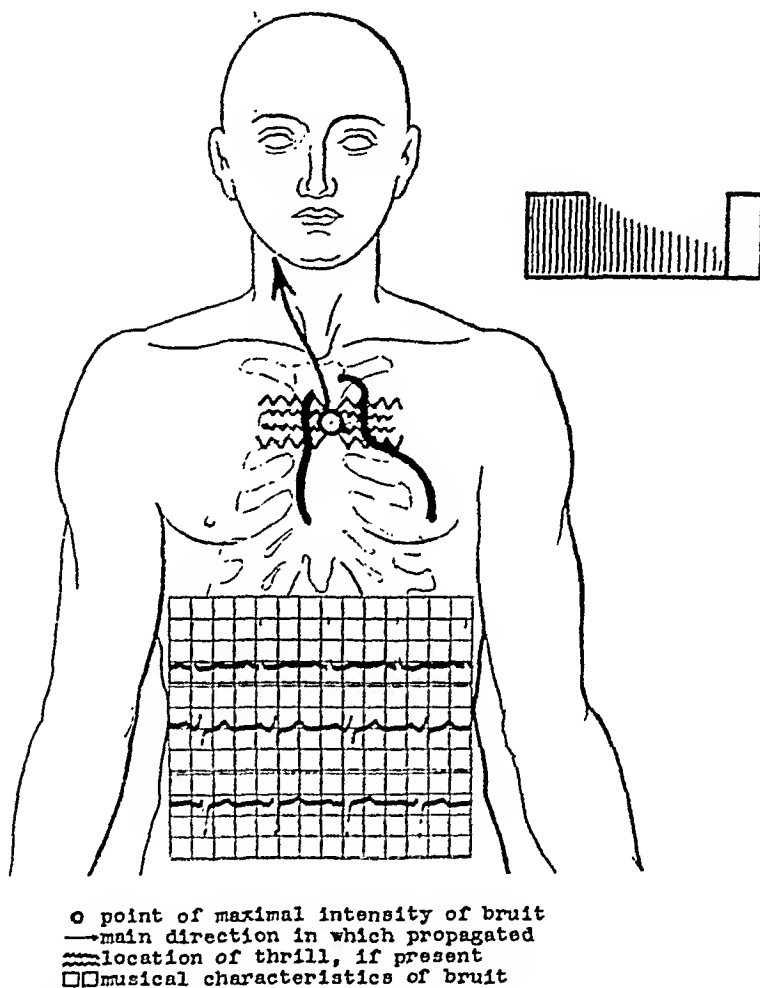


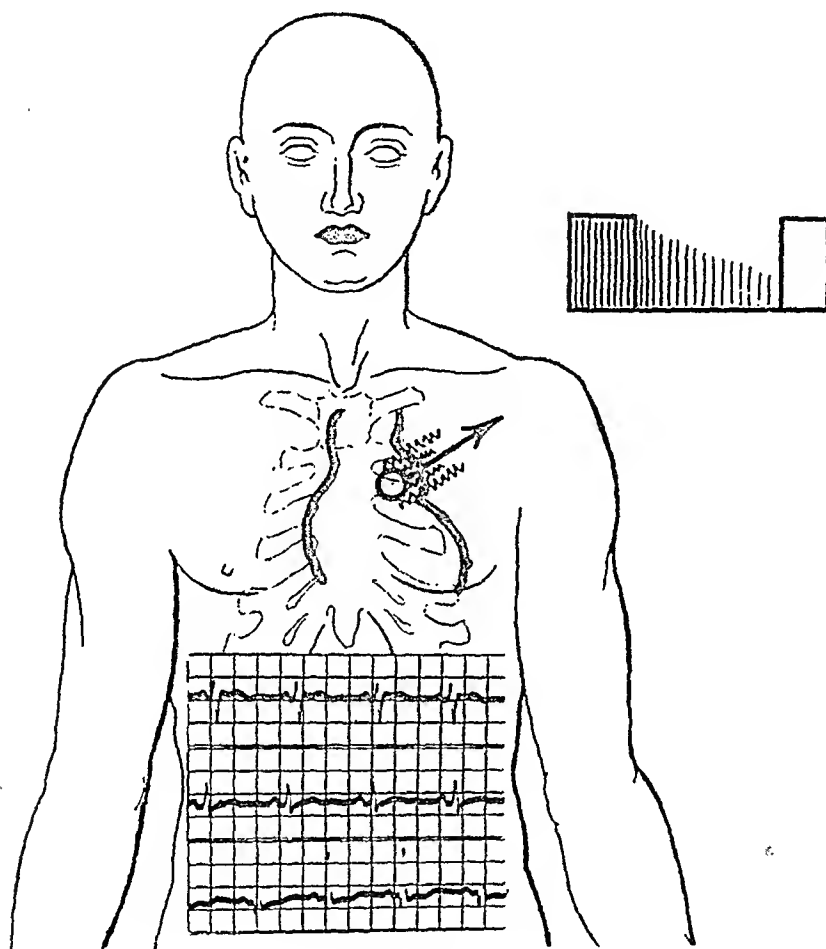
Fig. 7.—Subaortic stenosis. The left ventricle is hypertrophied and the electrocardiogram shows left axis deviation.

Comment. The prognosis is good.

*Pulmonary Stenosis.*—Mechanism. 1. With a closed interventricular septum, the right ventricle naturally hypertrophies markedly. Depending on the degree of the defect, cyanosis almost inevitably supervenes, although the individual may reach adult life before it becomes noticeable. Once it begins, it is likely to be progressive, with increasing clubbing and polycythemia. 2. With an interventricular septal defect (which is far more common), the load is taken off the right

ventricle to some extent, but cyanosis occurs earlier because of the venous-arterial shunt. In both instances the foramen ovale is likely to be patent, no doubt because of increased pressure on the right side of the heart; this may add to the venous-arterial shunt.

The syndrome. The syndrome consists of: (1) A harsh systolic bruit in the second left interspace, which is transmitted toward the left shoulder and not to the vessels in the neck, (2) a well-marked thrill, (3) a prominent conus, which is evidence of hypertrophy of the right



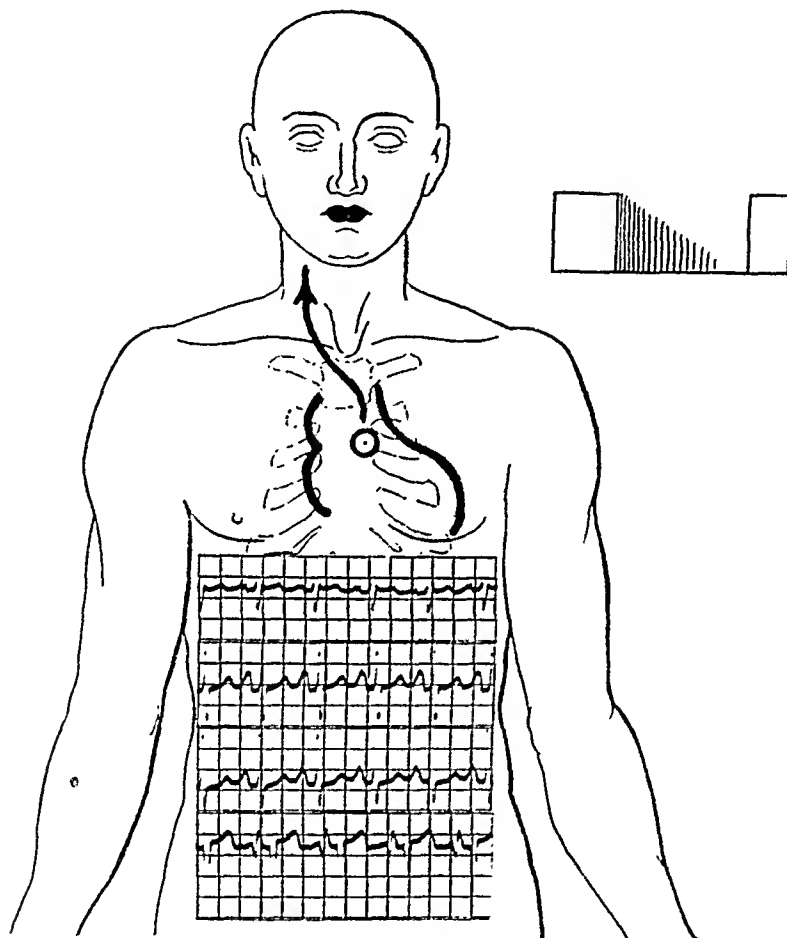
○ point of maximal intensity of bruit  
 — main direction in which propagated  
 ~ location of thrill, if present  
 □ musical characteristics of bruit

Fig. 8.—Pulmonary stenosis, showing the prominence of the conus shadow and the hypertrophied right ventricle. The electrocardiogram shows right axis deviation. The shading of the lips indicates cyanosis.

ventricle, and enlargement of the right auricle, (4) right ventricular strain electrocardiographically, and there may be T-wave changes in Leads II and III significant of right heart strain, and (5) cyanosis, sooner or later, with the usual secondary manifestations (Fig. 8).

Comment. Symptoms tend to develop early. Dyspnea on exertion heralds the manifestations associated with impaired oxygenation and myocardial damage. Not a few patients succumb to subacute bacterial endocarditis.

*The Tetralogy of Fallot.*—Mechanism. As the right ventricle empties itself, the smaller portion of venous blood enters the much narrowed pulmonary artery, whereas the major portion enters the large aorta which usually directly overrides the defect in the interventricular septum (Fig. 2). The venous blood which does get aërated returns to the left auricle and so to the left ventricle. With contraction of the latter, this aërated blood joins the stream of venous blood from the right ventricle in the aorta. It is apparent, then, that with the com-



● point of maximal intensity of bruit  
 → main direction in which propagated  
 ~~~ location of thrill, if present  
 □ musical characteristics of bruit

Fig. 9.—The tetralogy of Fallot: Note the boot-shaped heart, the right axis deviation in the electrocardiogram, with a positive T-wave in the fourth lead (Wolferth). The shading of the lips indicates cyanosis.

bined effects of the venous-arterial shunt and the much restricted pulmonary circulation, cyanosis will be prominent. The peribronchial vessels help, to a greater or lesser degree, to carry blood for aëration to the lungs, and the efficiency of this alternate route does a good deal toward establishing the prognosis in the individual case.

The syndrome. The syndrome is as follows: (1) Cyanosis tends to begin early in life and often becomes extreme, (2) bruits may be

absent, but there is usually a systolic murmur at the base transmitted to the vessels in the neck, with or without an accompanying thrill, (3) the heart becomes sabot-shaped because of the prominent right ventricle without enlargement of the pulmonary artery, and because of the dextroposition of the aorta, the great vessels will be prominent on the right, and (4) there is electrocardiographic evidence of right ventricular strain (Fig. 9).

*Patent Ductus Arteriosus.*—Mechanism. Because of the higher aortic pressure, blood is shunted from the aorta into the pulmonary artery.

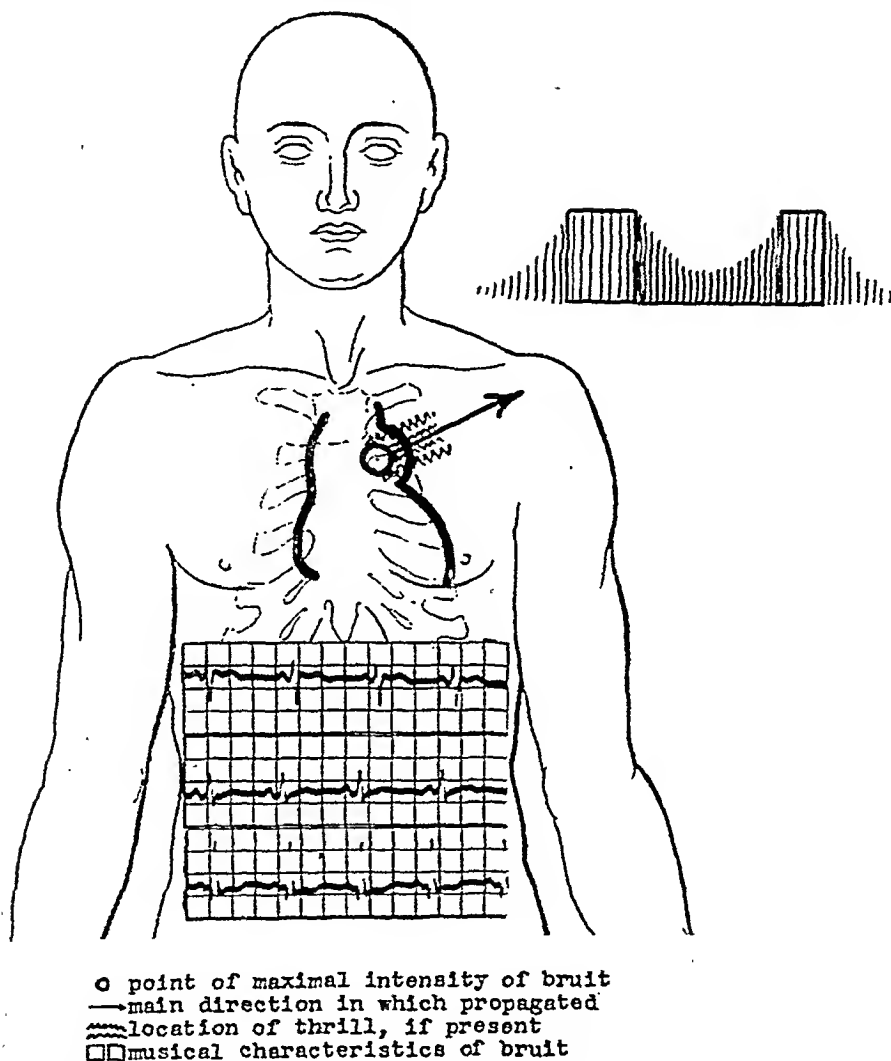


Fig. 10.—Patent ductus arteriosus (Botalli): Note the prominence of the conus shadow. The electrocardiogram shows right axis deviation.

While this is not particularly disadvantageous, it does increase the load on the right ventricle. When conditions arise which increase the pressure in the pulmonary circuit above the systemic level, a reversal of the shunt occurs, with cyanosis corresponding in degree and duration to the extent of the shunt.

The syndrome. The syndrome consists of: (1) A “machinery” or continuous murmur in the second left interspace which is transmitted toward the left shoulder, the second pulmonic sound usually being accentuated, (2) dullness in the region of the second and third left

interspaces (Gerhardt's ribbon dullness), (3) a prominent cone shadow, and (4) right axis deviation in the electrocardiogram (Fig. 10).

*Comment.* This is a typical example of a congenital lesion in which symptoms are absent in marked contrast to the prominent physical findings. The frequent development of subacute bacterial endocarditis renders the prognosis guarded, even though no serious mechanical difficulties are likely to develop.

*Coarctation of the Aorta.—Mechanism.* The obstruction to the aorta is usually just beyond the origin of the left subclavian artery, that

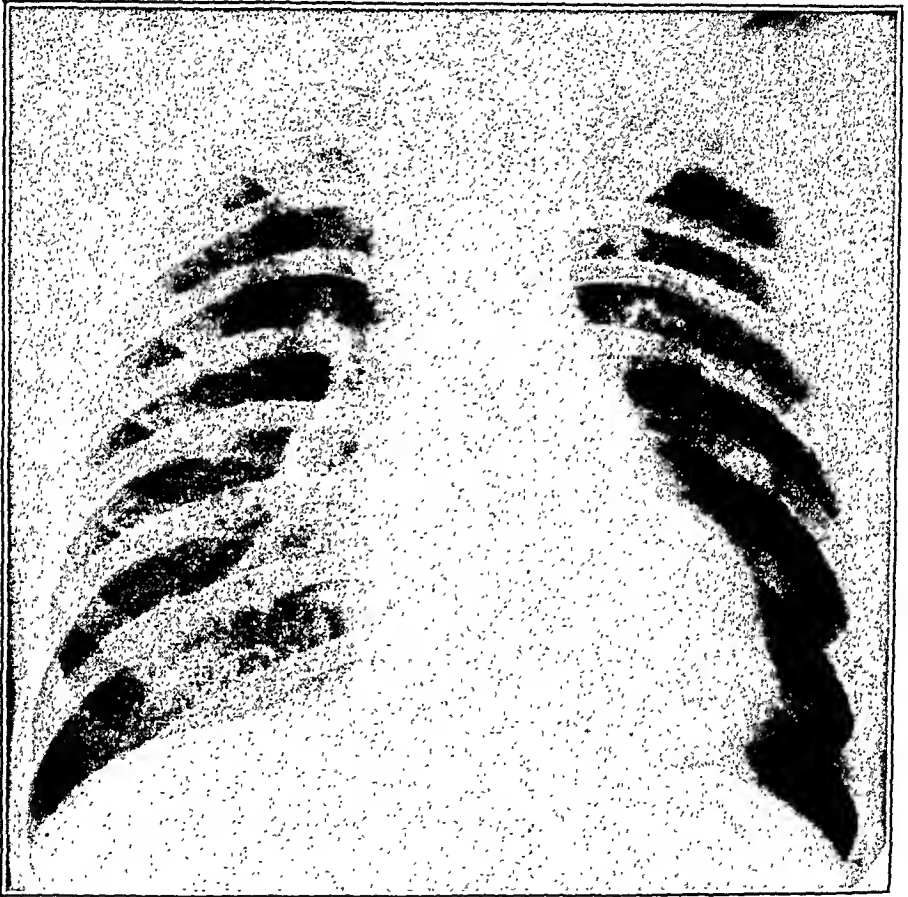


Fig. 11.—Roentgenologic appearance of coarctation of the aorta: Note the absence of the aortic knob and the erosion of many of the ribs. The left ventricle is hypertrophied.

is, at or near the junction of the ligamentum arteriosum and the aorta. The ligamentum arteriosum is the occluded ductus arteriosus, and it often remains patent when anomalies of the aortic arches are present. Interference with circulation beyond the point of obstruction depends (1) on the degree of coarctation, and (2) on the degree of collateral circulation which can be built up. The latter element, affecting mainly the intercostal arteries and the internal mammary artery and its branches, gives rise to characteristic clinical and roentgenologic findings in the form of pulsating vessels and erosion of the undersurface

of some of the ribs (Fig. 11). The obstruction also results in increased pressure in the vessels arising proximal to the point of obstruction. In these cases pulsations in the abdominal aorta and femoral vessels are markedly diminished in contrast to hypertension in the upper extremities.

The syndrome. The syndrome is as follows: (1) a systolic bruit is often present over the base and is easily confused with acquired aortic stenosis, (2) a thrill may accompany the bruit, (3) there is evidence of left ventricular hypertrophy, (4) there is electrocardiographic evidence of left ventricular strain, and (5) there is evidence of the collateral circulation just described.

Comment. Coarctation of the aorta may be latent for years, and congestive heart failure may first bring the patient to a physician. Very frequently, however, the condition terminates fatally as a result of the development of subacute bacterial endocarditis, and not a few patients die suddenly from a ruptured aneurysm of the circle of Willis, which is frequently an associated congenital anomaly. Many patients complain that their legs "go to sleep" very readily because of diminished circulation to the lower extremities. Others live to an advanced age and die from an unrelated cause.

*Persistent Right Aortic Arch.*—Mechanism: Physiologically the mechanism is perfectly normal and represents the avian arrangement. The abnormal anatomical situation, however, especially its relation to the trachea and esophagus, may cause symptoms of pressure referable to these structures.

The syndrome. The syndrome consists of (1) evidence that the ascending aorta is farther to the right than normal, namely, dullness to the right of the sternum, pulsation in the second or third right interspaces, maximal intensity of the aortic heart sounds to the right and above the usual location, and strong pulsations in the right supraclavicular fossa; and (2) characteristic roentgenologic findings, which are (a) a shadow to the right of the sternum running upward toward the right sternoclavicular joint, (b) evidence of displacement of the esophagus and trachea toward the left (this is well brought out by fluoroscopy with a barium-filled esophagus, whereas a stomach tube may be delayed at the point of displacement and transmit the pulsation from the arch of the aorta), (c) absence of the normal aortic knob in the usual situation and the presence of a retro-esophageal aortic knob determined by fluoroscopy, and (d) corroborative evidence is supplied by eliciting, fluoroscopically, a diverticulum-like structure joining the descending aorta which represents the fourth left arch beyond the point of origin of the ductus arteriosus (Fig 3).

Comment. In most of the cases described the heart is normal and symptoms may be entirely absent. So-called dysphagia lusoria resulting from esophageal displacement occurs but is frequently absent as in Arkin's cases.<sup>1</sup>



*Congenital Anomalies Which Are Rare But in Which the Diagnosis May Be Suspected.*—Anomalies of the coronary artery. McGinn and White<sup>6</sup> described the case of an infant who manifested attacks of distress on effort, such as when nursing, while the electrocardiogram showed T-wave changes of the coronary type. The heart was hypertrophied. At necropsy a single coronary artery was found arising from the pulmonary artery. The effects of anoxemia in this case were analogous to those in coronary occlusion.

Cor triloculare biatriatum. On the basis of another anomaly the same authors laid down the dictum that when in the roentgenogram a "water-bottle" shaped heart resembling a pericardial effusion is associated with intraventricular conductive disturbances in the electrocardiogram, a three-chambered heart of the foregoing type should be kept in mind.

#### THE PROGNOSIS IN CONGENITAL HEART DISEASE

It is not always easy to prognosticate the future course of congenital heart disease. There is, however, with a few reservations, no reason to deviate from the usual criteria for judging cardiac efficiency. The heart is essentially a muscular pump and its main function is to maintain adequate circulation under the varying conditions incident to the daily life of the individual. With this as a premise, and it is common to all cardiac states, and with the general principle common to the wider fields of diagnostic medicine that an isolated sign rarely has much significance, the degree to which this, its main function, is interfered with in the main establishes the prognosis.

The nature and degree of the mechanical disadvantage are the first considerations; hence, again, the importance of establishing an anatomical diagnosis. In states such as patent foramen ovale, patent ductus arteriosus, maladie de Roger, and subaortic stenosis, it may be practically negligible and in spite of loud murmurs there may be little if any interference with the patient's activity. When, however, the degree of altered function is such as to place undue strain on one or more chambers of the heart, hypertrophy, dilatation, and later, loss of cardiac reserve, must inevitably follow. This undue strain is mainly brought about by abnormal shunts of blood through incomplete septa or through stenotic orifices, and finally, through extracardiac factors such as increased pressure within the pulmonary circuit. Evidence of hypertrophy or enlargement of individual chambers or of the heart as a whole then definitely influences the prognosis adversely, according to the degree of such enlargement.

The reservations previously referred to are occasioned by the vulnerability of the congenitally anomalous heart to rheumatic fever, by the frequency with which subacute bacterial endocarditis becomes engrafted upon it, and by the sudden death of an individual in appar-

ently good health. Abbott's statistical studies supply enlightening information regarding the termination in various types of congenital heart disease.<sup>9</sup> Small interventricular septal defects with patent ductus arteriosus may interfere very little with activity, but in from 20 to 25 per cent of cases of both types subacute bacterial endocarditis develops. In contrast, a widely patent foramen ovale is hardly ever the basis for such a complication, but in about half the cases congestive failure eventually develops. For the group of cases in which lesions involve the pulmonary infundibulum, with or without associated ventricular septal defects and the different degrees of transposition of the great vessels, the prognosis is not good. Cyanosis is likely to develop early and to be progressive, and incapacitation is the rule. Subacute bacterial endocarditis terminates life in more than 20 per cent of this group.

The individual with coarctation of the aorta leads an existence beset with even more hazards. About a third of the patients die with congestive failure; subacute bacterial endocarditis claims about 10 per cent. An unexpected and dramatic termination is not infrequently the result of subarachnoid hemorrhage due to rupture of an aneurysm of the circle of Willis, and rupture of the proximal part of the ascending aorta not infrequently occurs. Of Abbott's seventy patients with the adult type of coarctation, twenty-two died suddenly. Headaches, convulsions, and other neurological complications have been commented on.<sup>3</sup>

In spite of mechanical disadvantages and unpredictable hazards, however, remarkable instances of longevity have been recorded: Thus Firket's patient,<sup>10</sup> a woman with combined mitral stenosis and an auricular septal defect, went through eleven pregnancies and three abortions and lived to the age of seventy-four; Lutembacher's patient,<sup>11</sup> also a woman and with the same type of lesion, lived to be sixty-one years old and went through seven pregnancies without heart failure, and two other patients with the same types of lesions lived to the age of seventy-four and sixty-two years, respectively.<sup>12</sup> White and Sprague's<sup>13</sup> case of the tetralogy of Fallot was even more remarkable: The patient, although cyanosed, lived a full life and died at the age of fifty-nine years and eight months. Erickson and Willius<sup>14</sup> reported a case of widely patent foramen ovale, so wide that a normal heart could be fitted snugly into the opening; yet the patient, a man, lived to be seventy-one years old.

#### SUMMARY AND CONCLUSIONS

A study of the embryology and comparative anatomy of the heart is essential in understanding the genesis and mechanism of human congenital cardiac anomalies. A number of these congenital lesions are recognizable clinically. The syndromes diagnostic or suggestive

of interventricular and interauricular septal defects, including Lutembacher's disease, subaortic and pulmonary stenosis, the tetralogy of Fallot, patent ductus arteriosus, coarctation of the aorta, persistent right aortic arch, one type of coronary artery anomaly, and the cor biatriatum trilobulare have been described.

While electrocardiographic evidence is important in the recognition of congenital heart disease, there is no diagnostic picture for any type except congenital dextrocardia with complete situs transversus.

The uncomplicated septal defects, patency of the ductus arteriosus, subaortic stenosis, and persistent right aortic arch may interfere with activity only to a limited extent, but the frequent occurrence of subacute bacterial endocarditis as a complication renders their prognosis guarded. Occasionally an individual with a gross cardiac defect lives to an advanced age.

#### REFERENCES

1. Arkin, A.: Double Aortic Arch With Total Persistence of the Right and Isthmus Stenosis of the Left Arch; New Clinical and X-ray Picture; Report of 6 Cases in Adults, *AM. HEART J.* 11: 444, 1936.
2. Baker, T. W., and Shelden, W. D.: Coarctation of the Aorta With Intermittent Leakage of a Congenital Cerebral Aneurysm, *Am. J. M. Sc.* 191: 626, 1936.
3. Woltman, H. W., and Shelden, W. D.: Neurologic Complications Associated With Congenital Stenosis of the Isthmus of the Aorta. A Case of Cerebral Aneurysm With Rupture and a Case of Intermittent Lameness Presumably Related to Stenosis of the Isthmus, *Arch. Neurol. & Psychiat.* 17: 303, 1927.
4. Abbott, Maude E.: Congenital Heart Disease. In: Nelson Loose-Leaf Medicine, New York, Thomas Nelson and Sons, vol. 4, p. 222.
5. Barnes, A. R., and Whitten, M. B.: Study of T-wave Negativity in Predominant Ventricular Strain, *AM. HEART J.* 5: 14, 1929.
6. McGinn, Sylvester, and White, P. D.: Progress in the Recognition of Congenital Heart Disease, *New England J. Med.* 214: 763, 1936.
7. Edeiken, Joseph, Wolfertli, C. C., and Wood, F. C.: The Significance of an Upright or Diphasic T-wave in Lead IV When It Is the Only Definite Abnormality in the Adult Electrocardiogram, *AM. HEART J.* 12: 666, 1936.
8. Roger, H.: Recherches cliniques sur la communication congénitale des deux coeurs, par inoclusion du septum interventriculaire, *Bull. de l'Acad. de méd.* 8: 1074, 1879.
9. Abbott, Maude E.: Congenital Heart Disease. In: Nelson Loose-Leaf Medicine, New York, Thomas Nelson and Sons, vol. 4, chart 1, p. 207.
10. Firket: Quoted by White, P. D.: Heart Disease, New York, 1931, The Macmillan Company, p. 473.
11. Lutembacher: Quoted by White, P. D.: Heart Disease, New York, 1931, The Macmillan Company, p. 473.
12. Bonnel: Quoted by White, P. D.: Heart Disease, New York, 1931, The Macmillan Company, p. 473.
13. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot. Report of a Case in a Noted Musician, Who Lived to His Sixtieth Year, *J. A. M. A.* 92: 787, 1929.
14. Erickson, C. W., and Willis, F. A.: Cardiac Clinics: Cardiopathy of Undetermined Origin: Enormous Cardiac Enlargement, Recurrent Congestive Failure, Heart Block, and Cerebral Embolism; Clinical and Post-Mortem Findings, *Proc. Staff Meet., Mayo Clin.* 11: 248, 1936.

## CHEST LEAD TRACINGS IN ARTERIAL HYPERTENSION WITH CARDIAC ENLARGEMENT

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**I**T IS the purpose of this presentation to call attention to a possible source of error in the interpretation of chest lead tracings in cases of arterial hypertension. In the conventional chest lead tracings,\* introduced by Wolferth and Wood,<sup>1</sup> the ventricular complex is described as consisting of a large diphasic QRS and a large negative T-wave. Although variations in this normal pattern are not uncommon, the actual variations are usually in amplitude only. One of the limbs of the QRS, either the Q or the R may be somewhat stunted, or the T-wave may show only a shallow inversion. However, in order that the tracing shall qualify as normal, its configuration may not be altered to a point where any one of its essential features is eliminated. The initial portion of the ventricular complex should have Q and R components and the T-wave should show at least a shallow inversion.†

Classical alterations in the ventricular complex of chest lead tracings, as pointed out by Wood et al.,<sup>2</sup> occur generally in cases of focal myocardial damage due to an occlusion along the course of the anterior descending branch of the left coronary artery. Such alterations include: (1) Elimination of the initial component of the QRS—absence of the Q wave, and (2) positive or upwardly directed T-waves. At this stage of our familiarity with chest lead tracings it is not necessary to cite literature to prove that such changes indicate myocardial damage. The pattern is accepted as corroborative evidence in cases where the history, and clinical findings suggest coronary occlusion. That the electrocardiogram is merely corroborative must be emphasized because chest lead tracings with upright T-waves, although a characteristic finding in anterior infarction, may be found in conditions other than actual cardiac infarction. Furthermore, they are not uncommonly found in apparently normal children.<sup>3</sup>

It is the purpose of this communication to point out that even in persons in the arteriosclerotic age group and even in those with anginal symptoms, abnormal T-waves in chest lead tracings must be evaluated with considerable caution. That is, an upright T-wave in the conventional chest lead tracing may not always be taken as an indication of a focal myocardial damage even when there are other evidences of coronary artery disease. The electrocardiographic pattern in arterial hypertension with cardiac enlargement is of special interest in this connection.

In this type of heart disease the standard electrocardiogram is often of a distinctive pattern.<sup>4, 5, 6</sup> It shows: (1) Moderately high voltage,

\*Lead IV and/or Lead V.

†There are exceptions to this in the case of young children and, rarely, in the case of seemingly normal adults.

(2) left axis deviation, (3) inversion of  $T_1$ , and (4) a tall, upright  $T_3$ . Of course this is not, strictly speaking, a pattern of hypertension. It is the pattern rather of an enlarged and hypertrophied left ventricle which develops in a long-standing hypertension. Extreme left heart enlargement due to other causes may produce a similar pattern.

Chest lead tracings recorded from the region of the apex beat in arterial hypertension with cardiac enlargement may present a confusing picture. The reason, as indicated, is apparently anatomical.

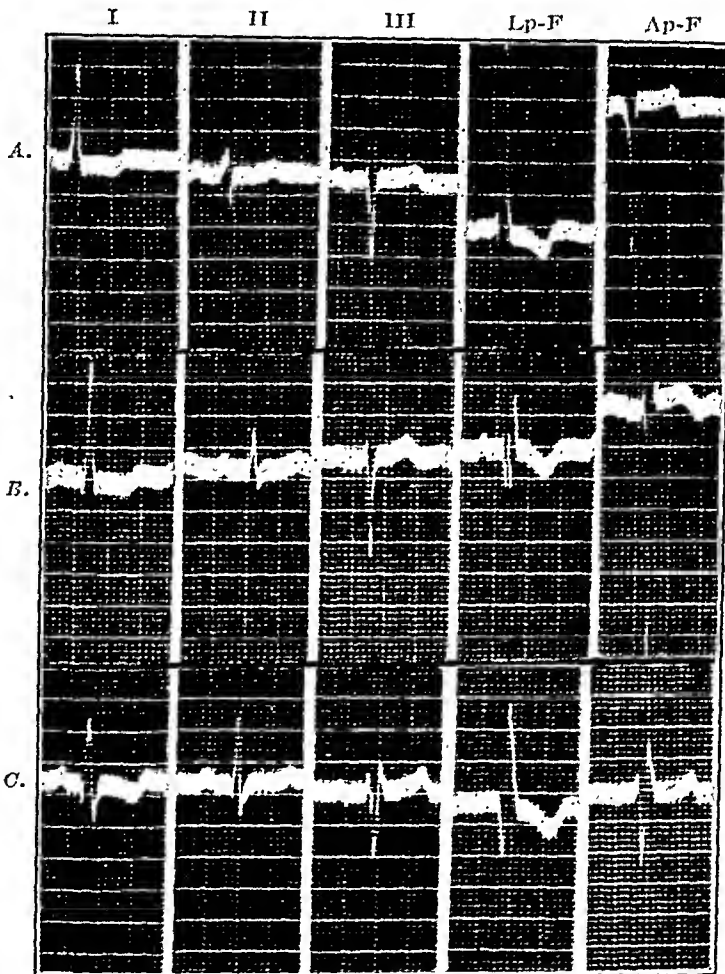


Fig. 1.—Standard Leads I, II, III, and chest leads, Left pectoral-Foot (*Lp-F*) and Apex-Foot (*Ap-F*). *A*, *B*, and *C* represent cases of arterial hypertension with cardiac enlargement. In each case  $T_1$  shows inversion of its first portion, and  $T_3$  is upright. The *Lp-F* chest lead shows a negative T-wave (normal pattern) and the *Ap-F* chest lead shows an upright or partly upright T-wave, resembling in general standard Lead III.

The outermost border of the left ventricle in this type of disorder often extends to or beyond the anterior axillary line. Consequently, a chest lead taken with the exploring electrode at the apex is really an axillary lead and not a pectoral lead. Axillary leads in normal persons are known to resemble standard limb leads and the axilla-foot lead of the group resembles standard Lead III. Chest lead tracings, therefore, in which the exploring electrode is situated near the axilla,

yield a record of a modified, often a magnified, standard Lead III. But, as has been pointed out above, the pattern of standard Lead III in arterial hypertension with cardiac enlargement is often characterized by a conspicuous upright T-wave. Consequently, the apical chest lead tracing, which is really an axillary tracing, also presents an upright T-wave. This may lead to confusion if we attempt to evaluate such a tracing unconditionally in the light of criteria established for normal apical chest lead tracings.

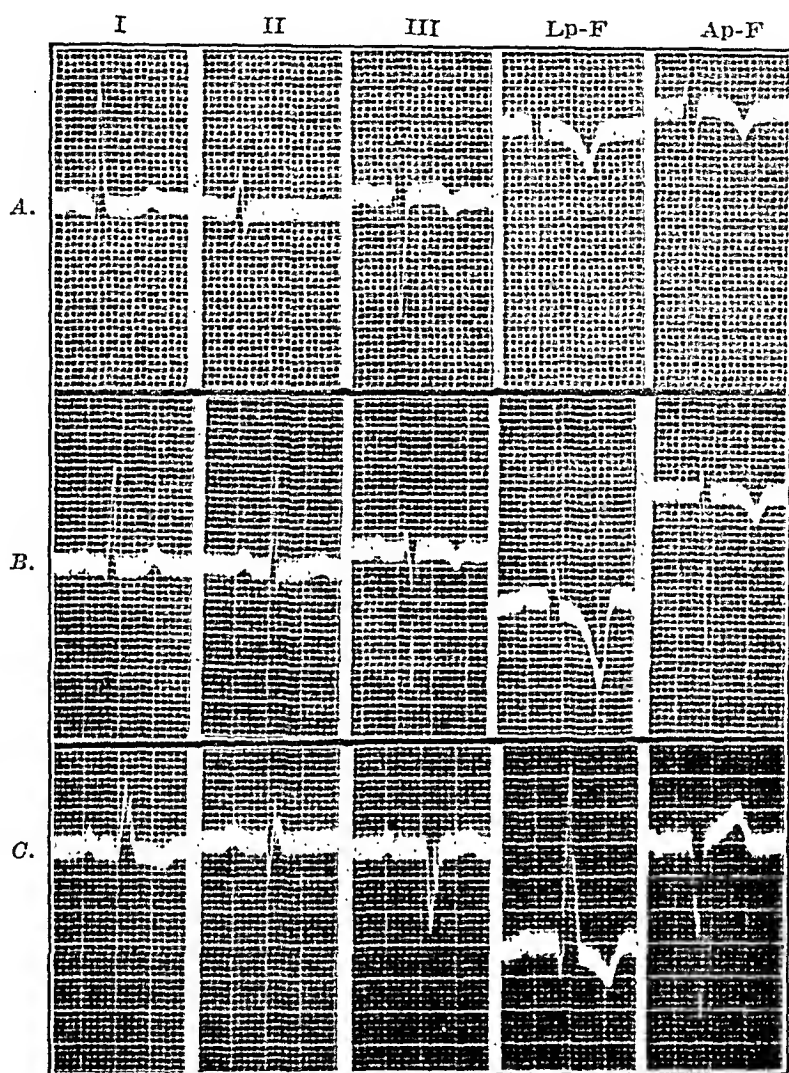


Fig. 2.—Standard Leads I, II, III, and chest leads, Left pectoral-Foot (Lp-F) and Apex-Foot (Ap-F). A and B represent cases of rheumatic aortic insufficiency with left heart enlargement.  $T_3$  is negative in both. C represents a case of rheumatic aortic insufficiency and mitral insufficiency with a typical cor bovinum in a young man thirty-two years of age.  $T_3$  is upright. Systolic blood pressure is only moderately elevated in these cases. As in Fig. 1, here too, the Ap-F chest lead resembles standard Lead III in each case.

Examples of such cases are presented in Fig. 1. Each case is represented by standard Leads I, II, and III, a left pectoral chest lead\* and an apical chest lead. The standard leads are seen to conform to the pattern described. The left pectoral chest lead conforms to criteria established for normals. The apical chest lead, on the other hand, shows a large negative component in the QRS and a conspicu-

\*Exploring electrode situated midway between the sternum and midclavicular line.

ous upright T-wave. It resembles standard Lead III. This is one of the chest lead patterns in arterial hypertension with cardiac enlargement.

In order to show that the abnormal T-wave is probably due to the axillary application of the exploring electrode necessitated by the displacement of the apex impulse as a result of cardiac enlargement, cases with left heart enlargement due to causes other than arterial hypertension were chosen for comparison. These are presented in Fig. 2. Graphs *A* and *B* each represent a case of rheumatic aortic insufficiency with only a moderate systolic hypertension, not above 160 mm. in either case. In these the T-waves in Lead III of the standard electrocardiogram are negative. Graph *C* represents a case of rheumatic aortic and mitral insufficiency with systolic pressure well within the upper limit of normal. In this case, standard Lead III shows an upright T-wave. Because of marked displacement of the left border of the heart, the apex chest lead in this group had to be taken with the exploring electrode situated at or near the anterior axillary line. As seen in the figure, the ventricular complexes of the apex chest lead tracings resemble those of standard Lead III in each case. In graphs *A* and *B*, the ventricular complex shows an inverted T-wave while in graph *C* the T-wave is upright.

In clinical electrocardiography, especially in the busy laboratory, where daily reporting of tracings is a pressing task, there is a tendency to lean on cardiographic patterns as a matter of convenience in routine reporting. Criteria for diagnosis are eagerly sought and are often employed without a knowledge of the clinical history or physical findings in the case. Electrocardiographic "evidences of myocardial damage" are often reported on findings less convincing than T-wave changes in chest lead tracings. Consequently, upright T-waves such as are seen in the apex chest lead in certain cases of arterial hypertension with cardiac enlargement may naturally prompt a diagnosis of myocardial infarction. It is realized that cases of hypertensive heart disease often have sclerosis of the coronary arteries and, at times, even myocardial infarction, but it must be emphasized that the upright T-wave seen in the apex chest lead in such cases *may not* be taken as the criterion upon which to base the diagnosis.

In a previous publication<sup>7</sup> it has been pointed out that in selecting the site of application of the exploring electrode in chest leads, the apex, because of its elusiveness, is perhaps the least reliable site. In persons of middle age it is at times difficult to locate the apex beat with any degree of accuracy. We may now add that the so-called apex lead in cases of arterial hypertension at times yields a tracing of an actually deceptive pattern in that it includes an upright, abnormal T-wave which may lead to a faulty diagnosis.

On the other hand, as the tracings in Figs. 1 and 2 show in cases of arterial hypertension with cardiac enlargement, even of a degree sufficient to produce a distinctive pattern in the standard leads, the



left pectoral chest lead tracing is not appreciably altered. This is of considerable importance. It is well known that in coronary occlusion of the anterior type, it is precisely this lead which shows the most marked T-wave changes. Consequently, the left pectoral chest lead may be used for the purpose of a differential diagnosis in cases of left heart enlargement when a myocardial infarction is suspected. Furthermore, as has been said, the electrocardiographic pattern of the apical chest lead in hypertensive heart disease is characterized by a QRS which has a large negative component. In cardiac infarction, on the other hand, due to thrombosis along the course of the anterior left descending coronary artery, the left pectoral chest lead tracing is generally characterized by a complete absence of the negative component. The contrast between the patterns of the left pectoral and apex chest leads in arterial hypertension with cardiac enlargement is conspicuous.

#### SUMMARY

An electrocardiographic pattern of the apical chest lead tracing in certain cases of arterial hypertension with cardiac enlargement has been presented. The ventricular complex in this tracing is characterized by a QRS which consists predominantly of a large negative component and by an upright T-wave. The pattern is essentially a modified standard Lead III, and is due, apparently, to the axillary situation of the exploring electrode.

Examples of left heart enlargement in cases of rheumatic aortic insufficiency, some having negative, others positive, T-waves in standard Lead III, are presented for comparison to show that in these cases too, the apical chest lead tracing resembles standard Lead III.

The left pectoral chest lead tracing is not appreciably altered in these cases, and, therefore, stands out in marked contrast with the apical lead. This lead, therefore, may serve in problems of differential diagnosis. In fact, the left pectoral lead is the chest lead of choice and the so-called apical lead should be avoided as a routine lead in cases of arterial hypertension with left heart enlargement.

#### REFERENCES

1. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.
2. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion: Further Observations on the Use of Chest Leads, *Arch. Int. Med.* 52: 752, 1933.
3. Rosenblum, H., and Sampson, J. J.: A Study of Lead IV of the Electrocardiogram in Children With Special Reference to the Direction of Excursion of the T-Wave, *AM. HEART J.* 11: 49, 1936.
4. Luten, D., and Grove, E.: Incidence and Significance of Electrocardiograms Showing Features of Left Axis Deviation and QRS of Normal Duration With Inverted T, and Upright T<sub>s</sub>, *AM. HEART J.* 4: 431, 1929.
5. Master, A. M.: Characteristic Electrocardiograms and Roentgenograms in Arterial Hypertension, *AM. HEART J.* 5: 291, 1930.
6. Rykert, H. E., and Hepburn, H.: Electrocardiographic Abnormalities Characteristic of Certain Cases of Arterial Hypertension, *AM. HEART J.* 10: 942, 1935.
7. Roth, Irving R.: On the Use of Chest Leads in Clinical Electrocardiography, *AM. HEART J.* 10: 798, 1935.



## CORONARY AND EXTRACORONARY FACTORS IN HYPERTENSIVE HEART FAILURE\*

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CONGESTIVE heart failure is a common sequel of long-standing hypertension. Various physiological and pathological factors, such as coronary sclerosis, myofibrosis cordis, strain and fatigue, have been assigned rôles in heart failure of this type. The evidence that there is no histological equivalent for cardiac insufficiency or failure has been epitomized by Asehoff and Tawara.<sup>1</sup> More recently, since anatomical and physiological considerations have left the question open, attention has been paid to the rôle of metabolic disturbances in the causation of the failure of the hypertensive heart. In this study, the factors concerned in the failure of hypertensive hearts free of significant coronary disease have been considered. As a control group, a series of 40 hypertensive cases with chronic congestive heart failure and varying degrees of coronary artery disease have also been analyzed.

### MATERIALS

Congestive heart failure was considered to have been present when there was a history or signs of paroxysmal dyspnea or pulmonary edema, or when there was fluid retention manifested by hepatic or pulmonary congestion and latent or visible edema. The material comprised 21 cases of hypertension with congestive heart failure and minimal coronary disease and no gross myocardial damage, 40 with congestive heart failure and varying degrees of coronary disease, 8 hypertensive cases with coronary disease and no congestive heart failure, and 8 normal hearts. Numerous cross-sections of the hearts were made along the longitudinal courses of the coronary arteries. Blocks of tissue were taken from those areas which are frequently the sites of cardiac infarction, namely: (1) the junction of the upper and middle thirds of the interventricular septum, (2) the interventricular septum at the apex, (3) the apical region of the right ventricle, (4) the apical region of the left ventricle, (5) the posterior mitral region, and (6) the anterior papillary muscle of the left ventricle in some cases.

Paraffin sections were stained with hematoxylin-eosin and Verhoeff-van Gieson's mixture. Particular attention was paid to muscle fiber hypertrophy, to the presence or absence of increased or dilated sinusoids and to myocardial fibrosis. Attention was also paid to the relationship of vascular lesions to myocardial fibrosis. Since separation of the branches of the coronary arterial tree by muscle hyper-

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trophy may play a rôle in congestive heart failure by producing anoxemia, the number of arterioles per unit area of heart tissue was counted. A summary of these counts is reproduced in Table I.

#### FINDINGS

*Pathological.*—The coronary arteries of persons in the fourth decade commonly show changes when these individuals have had neither history nor signs of arteriosclerotic heart disease. Since we are dealing with cases at or beyond middle life and furthermore since hypertension hastens the tempo of development of arteriosclerosis, there was in no case complete absence of degenerative coronary artery disease. In that sense, there is no hypertension without coronary arteriosclerosis.

TABLE I  
ARTERIOLE COUNTS

| HEART WEIGHT IN GRAMS | NUMBER OF CASES | AVERAGE NUMBER OF<br>ARTERIOLES PER LOW<br>POWER FIELD<br>(AVERAGE OF 10 FIELDS) |
|-----------------------|-----------------|--|
| 200 to 300            | 9               | 3.14   |
| 300 to 400            | 5               | 2.20   |
| 400 to 500            | 4               | 1.42   |
| 500 to 900            | 10              | 1.13   |

*Histology of Myocardial Hypertrophy.*—Cardiac hypertrophy, macroscopic and microscopic, is the finding common to practically all cases of chronic congestive heart failure. This hypertrophy is due, according to Karsner, Saphir, and Todd,<sup>2</sup> solely to an increase in size of the individual fibers, since there is no actual increase in their number. The enormous size attained by some of the hypertrophied fibers may be seen by direct comparison with the normal fiber under the camera lucida, Fig. 1. The myofibrillae themselves are thicker than normal. The outline of the hypertrophied muscle fiber is frequently irregular, due to infoldings of the surface. The normal shallow grooves or slits may become so deepened that the enlarged fiber appears scalloped in cross-section. It is possible that this surface irregularity of the hypertrophied muscle fiber serves the physiological purpose of increasing the surface for greater diffusion of oxygen and metabolites. The presence of blood capillaries in the bottom of these grooves, Fig. 1 C, would favor the view that this is an additional adaptive mechanism.

The nuclei of the hypertrophied muscle fibers show profound changes. The nucleus of the normal muscle fiber shows some degree of surface irregularity and both binucleated and multinucleated forms occasionally occur. The changes in the early phases of cardiac hypertrophy are slight increases in the size of nuclei, squaring of their ends, and irregularities of contour. The nuclear changes in the hypertrophied fiber are merely an accentuation of the normal irregularity.

They were observed as far back as 1889 by Tangl,<sup>3</sup> though there has been no agreement as to their significance. As the nuclei increase in size progressively, they assume bizarre shapes, becoming elongated, square, C-shaped, or even totally irregular. On cross-section, this change is even more evident. All gradations from slight surface wrinkling to extensive stellate branching are seen. There is a rough

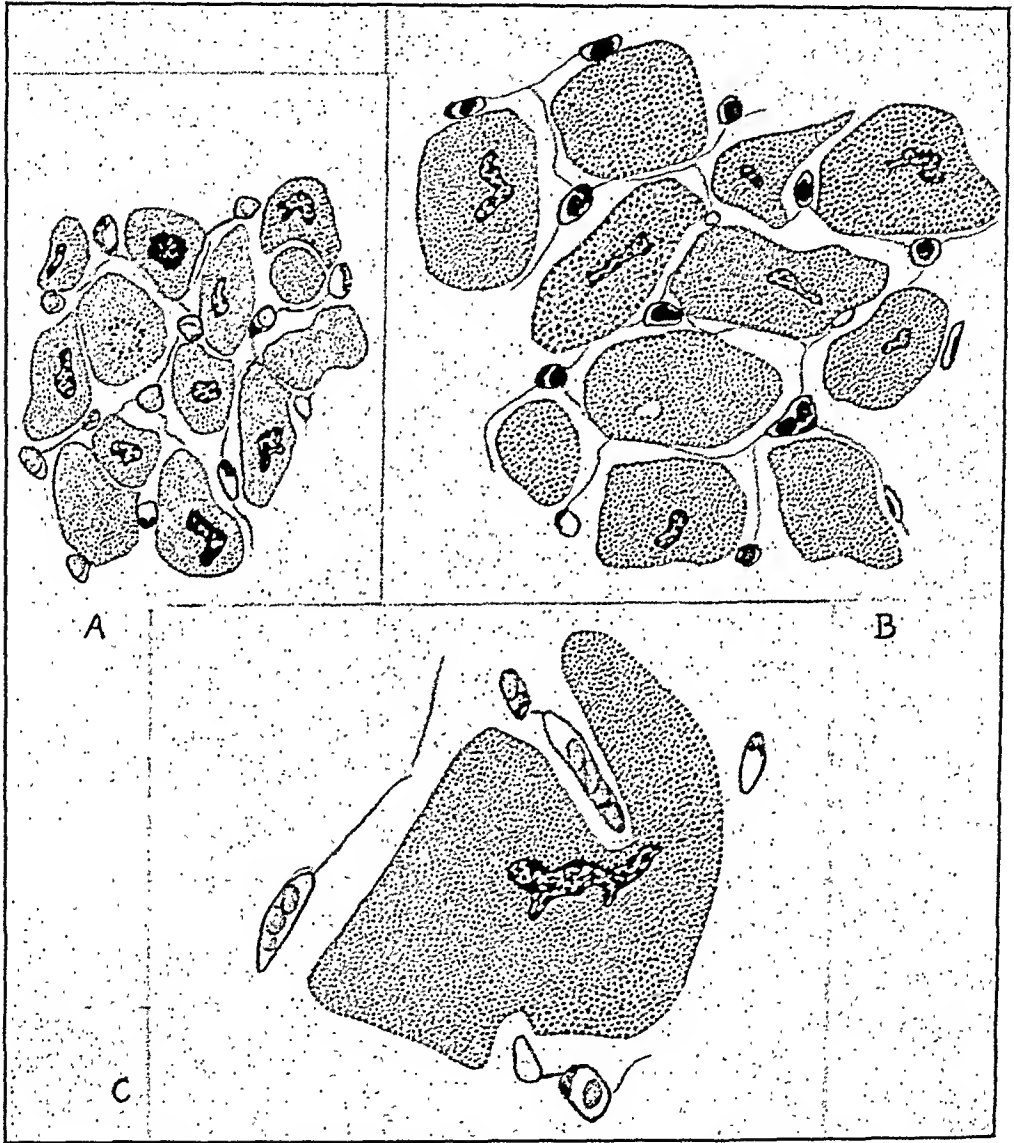


Fig. 1.—Camera lucida drawings of cross-sections of muscle fibers from the left ventricle, reproduced on the same scale. Magnification of approximately 400 diameters.

A.—Normal heart. Weight 300 gm.

B.—Hypertrophied heart. Weight 600 gm.

C.—Hypertrophied heart. Weight 750 gm.

Note the relationship between the capillary bed and the cross-sectional area of myocardium. The huge muscle fiber in Fig. 3 is not unusual in marked cardiac hypertrophy.

direct relationship between fiber size and nuclear irregularity, the largest fibers having the most bizarre nuclei. It seems to us that

these nuclear alterations represent an attempt to increase the surface area of the nucleus in order to provide for a better interchange of metabolites.

The chromatin content of the hypertrophied nucleus is usually increased, though at times it is diminished. Cohn<sup>4</sup> has observed a decrease in chromatin in cardiac hypertrophy.

Enlargement of the muscle fibers results also in a change in the nucleosarcoplasmic ratio. Collier<sup>5</sup> noted no change in nucleosarcoplasmic ratio in slight cardiac hypertrophy in dogs and rats. Preliminary quantitative measurements of this ratio in our material showed alterations due to a preponderance in volume of sarcoplasm in marked hypertrophy, and inconstant variations in the ratio in slight to moderate cardiac hypertrophy.

A striking feature of the histological picture of the hypertrophied myocardium is the paucity of arterioles and small arteries per unit area of heart muscle. Counts were made in 28 cases. In normal and enlarged hearts, counts of these vessels showed that there was roughly an inverse relationship between the size of the heart and the number of arterioles and small arteries per unit area.

Capillary counts were made by Wearn<sup>6</sup> who found an average of one capillary per muscle fiber in the normal heart. However, in the hypertrophied heart, the average per unit area is much less. The relationship between capillary bed and volume of myocardium supplied is graphically illustrated in Fig. 1. This fact, noted by us in hypertrophied human hearts, was recently confirmed experimentally by Shipley et al.<sup>7</sup>

There was no constant relationship between coronary arteriosclerosis and myocardial fibrosis. Every case of cardiac hypertrophy showed some increase of connective tissue, even though it may have been extremely slight. This increase in connective tissue was not directly dependent on coronary arteriosclerosis. In a control group of 8 hearts from patients of middle and advanced ages, there was an absence of even microscopic scarring in most instances. In almost all cases of cardiac hypertrophy, in which no scarring was evident microscopically, some degree of myofibrosis was seen on microscopic examination. Frequently, the area of scarring was of the width of only several muscle fibers, and in a few instances, the areas were almost macroscopic. Varying proportions of elastic tissue were present in the scars.

At least three types of histological changes were observed in the development of myocardial fibrosis. These were: (1) microscopic areas of coagulation necrosis, constituting miniature acute infarcts, similar in all respects to gross cardiac infarction following major coronary occlusion. All stages of replacement fibrosis were noted. This change was preceded by an ingrowth of granulation tissue which

finally became poor in fibroblasts and capillaries. (2) A slower process of fiber dissolution, namely, fatty degeneration terminating in cell death. In areas of varying microscopic size, all gradations were noted from accumulation of vacuoles within the muscle fibers to replacement by granulation tissue. Nuclear pyknosis and fragmentation accompanied the advanced stages of fatty degeneration. In the terminal phase, the muscle fiber consisted of a cell membrane, fat vacuoles and a fragmented pyknotic nucleus. Cell death was followed by invasion of macrophages, capillaries, and fibroblasts. The end stage of this process in the myocardium was replacement fibrosis. (3) The third type of change was seen in the very large hearts and consisted of a loss of myofibrillae with an insensible merging of connective tissue and muscle fibers. The resulting scars were as small as the width of single muscle fibers.

The perivascular connective tissue was increased in most instances of cardiac hypertrophy. This alteration was independent of myocardial fibrosis and represented a thickening of the connective tissue framework of the heart.

We observed an abundance of sinusoids in many instances of cardiac hypertrophy both with and without coronary artery disease. These were more conspicuous in the hypertrophied than in the normal heart. They arise by a widening of pre-existing channels and consist of a single layer of endothelium. A gradual transition may be seen between the sinusoids and the veins entering the epicardium. The sinusoids are numerous at the apical portion of the interventricular septum and the lower half of the left ventricle and are most numerous in the inner half of the myocardium where they empty into the pockets of the trabeculae carneae. Hearts weighing from 400 to 500 gm. had a slight increase of sinusoids, while those weighing more than 500 gm. frequently had a marked increase of sinusoids. Only a few red blood cells are seen in the lumens of these vessels and in but a few instances have we observed them to be engorged with blood.

Inconstant medial hypertrophy was noted in the smaller arteries and arterioles. This appears to be a compensatory mechanism in hypertensive hearts. The myocardial branches rarely showed changes other than slight reduplication of the internal elastic lamella, which, in addition, often showed splitting and irregularity.

#### SUMMARY OF CLINICOPATHOLOGICAL FINDINGS

Twenty-one patients had, grossly, minimal coronary artery disease. Of these, 13 had minimal coronary artery disease, both macroscopically and microscopically. Four were males and 9 were females. The heart weights varied between 420 and 880 gm., the average weight being 661 gm. In only 6 of the 13 was congestive heart failure less than two years in duration. In the majority, the failure lasted up to ten years. No correlation, however, could be made between heart weight

and duration or severity of failure. Evidently, some factor besides heart weight determines the onset of congestive heart failure.

In the remaining 8 patients, the coronary arteries were soft and grossly showed minimal arteriosclerosis, but microscopically, there were stenosing plaques of varying size. These cases comprised 5 males and 3 females. The heart weights varied between 520 and 1,050 gm., the average being 672 gm. Despite greater coronary disease, there



Fig. 2.—All sections from the left ventricle.

A.—Heart weight 880 gm.  $\times 60$ . Shows thickening of the medial coat in a medium sized myocardial artery.

B.—Heart weight 540 gm.  $\times 240$ . Marked coronary arteriosclerosis with occlusion of left circumflex artery. Several sinusoids are shown.

C.—Heart weight 380 gm.  $\times 240$ . Slight coronary arteriosclerosis. Several branching sinusoids may be noted.

D.—Heart weight 600 gm.  $\times 240$ . Minimal coronary arteriosclerosis. Four parallel sinusoids are shown.

was no relationship, however, between the severity and duration of heart failure and heart weight. It is noteworthy in this group, despite slightly greater coronary atherosclerosis, that congestive heart failure lasted longer than in the group with minimal coronary disease.

The causes of death in the first group of 13 were cerebral accidents in five and cardiac failure in three. The remainder had uremia or bronchopneumonia, and one died of a surgical complication. The causes of death in the eight cases with partially occluding plaques in the coronary arteries were congestive heart failure in two, sudden death in one, and bronchopneumonia or surgical complications in the remainder.

As a control group, 40 patients with congestive heart failure and varying degrees of coronary arteriosclerosis or thrombosis and myocardial infarction were studied. Divided according to sex, there were

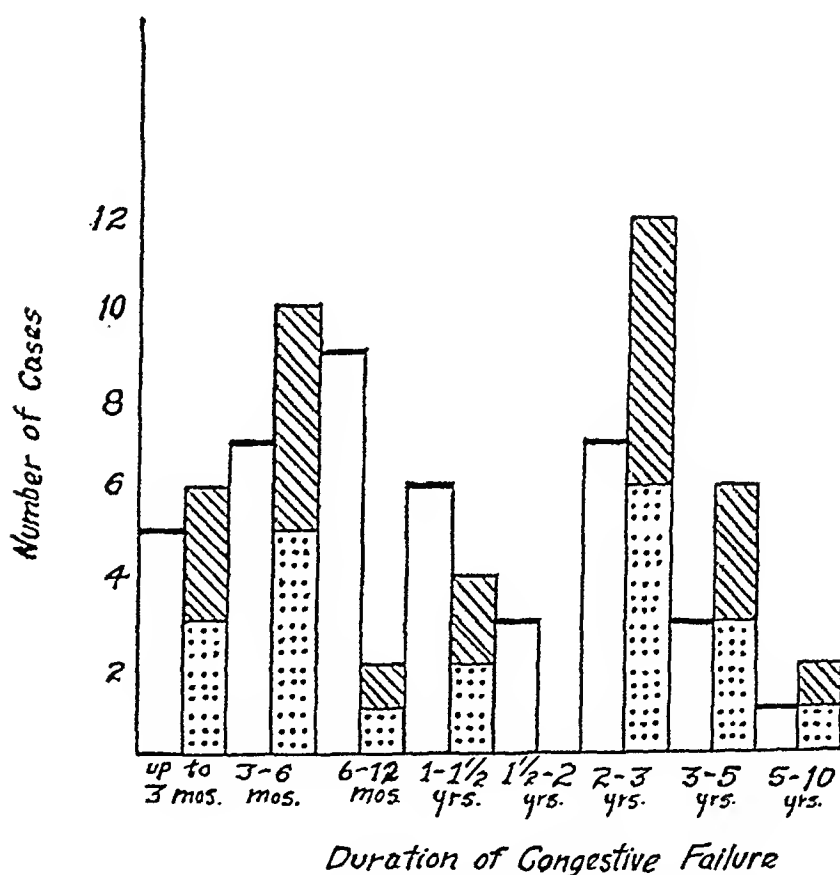


Fig. 3.—Showing duration of congestive heart failure in cases with and without major coronary arteriosclerosis. Table corrected for comparison of equal number of cases. Open spaces indicate number of cases of major coronary disease. Dotted boxes indicate number of cases of minimal coronary disease. Cross-hatched boxes indicate corrected number of cases of minimal coronary arteriosclerosis.

21 males and 19 females. Though hypertension is more common in women, the combination of hypertensive arteriosclerotic heart disease is usually severer and runs a shorter course in males. This was also the case in our material.

Cardiac hypertrophy was present in all but one case and is to be attributed to essential hypertension, since coronary disease alone does not cause cardiac hypertrophy. Of five cases of failure in hearts weighing less than 400 gm., failure was late in onset and was mild

in all. Two of these patients died in uremia which may have been a determining cause of water retention. The causes of death of the entire group are tabulated in Table II.

TABLE II  
CAUSES OF DEATH IN 40 CASES OF CONGESTIVE HEART FAILURE ASSOCIATED  
WITH SEVERE CORONARY DISEASE

|  |    |
|--|----|
| Bronchopneumonia .....   | 10 |
| Congestive heart failure.....  | 8  |
| (of these, one had bronchopneumonia and<br>another, terminal uremia) |    |
| Uremia .....   | 6  |
| Cerebral .....   | 5  |
| Sudden unexplained .....   | 5  |
| Convulsions .....  | 2  |
| Postoperative cardiac failure.....                                   | 1  |
| Following an anginal seizure.....                                    | 1  |
| Following an acute coronary thrombosis.....                          | 1  |
| Pulmonary edema .....  | 1  |
| Total  | 40 |

In another control group of 8 patients with essential hypertension with moderate and, in some cases, severe coronary artery disease and varying degrees of myocardial damage, congestive heart failure did not occur. The heart weights in all but two were 400 gm. or less. The heart weights of these two were 500 and 550 gm. In this group, there was also no correlation between myocardial scarring and vessel damage. The average heart weight of the cases of severe coronary disease with congestive heart failure was 554 gm., and is definitely lower than the average heart weight of cases with minimal coronary artery disease. Evidently, in the presence of coronary arteriosclerosis, the hypertensive cardiac patient dies from congestive heart failure and other causes often before the heart becomes massive.

Progressive or sudden additional coronary narrowing is associated with an impairment of nutrition responsible for more or less acute congestive heart failure in many cases of cardiac hypertrophy and occurred six times. Reference to Fig. 3 shows strikingly that in patients with severe coronary disease, the duration of failure was distinctly shorter than in those with minimal coronary sclerosis. In only 27.5 per cent of the cases with severe coronary disease was the duration of failure over two years. It is noteworthy that of all the hearts in failure weighing 500 gm. or more, 61 per cent had minimal coronary artery disease, Fig. 4. In both groups of cases, however, there was no correlation in any individual case between heart weight and duration of failure, nor was there a relation between muscle and vessel damage and failure. These facts point to the rôle of extracoronary vascular factors in hypertensive heart failure.



TABLE III  
RELATION OF DURATION OF CONGESTIVE HEART FAILURE TO HEART WEIGHT IN THE PATIENTS WITH MAJOR AND MINIMAL CORONARY ARTERY DISEASE

|             | LESS THAN 400 gm. |     | 400 TO 500 gm. |     | 500 TO 600 gm. |     | 600 TO 700 gm. |     | 700 TO 800 gm. |     | 800 TO 900 gm. |     | OVER 900 gm. |     |
|-------------|-------------------|-----|----------------|-----|----------------|-----|----------------|-----|----------------|-----|----------------|-----|--------------|-----|
|             | SCD*              | MCD | SCD            | MCD | SCD            | MCD | SCD            | MCD | SCD            | MCD | SCD            | MCD | SCD          | MCD |
| Up to 3 mo. |                   |     | 1              | 1   | 2              | 1   | 1              |     |                |     | 1              |     | 1            |     |
| 3 to 6 mo.  |                   |     | 4              | 1   | 1              | 1   |                |     |                |     | 1              |     |              |     |
| 6 to 12 mo. | 3                 |     | 2              |     | 1              |     | 2              |     | 1              |     |                |     |              | 1   |
| 1 to 1½ yr. | 1                 |     | 2              |     | 2              | 1   | 1              | 2   |                |     |                |     |              |     |
| 1½ to 2 yr. |                   |     | 1              |     | 2              |     |                | 1   |                |     | 1              |     |              |     |
| 2 to 3 yr.  |                   |     | 1              |     | 1              |     |                |     |                |     |                |     |              |     |
| 3 to 5 yr.  |                   |     | 1              |     | 1              | 3   | 4              | 1   |                | 1   |                |     |              |     |
| 5 to 10 yr. |                   |     |                |     | 2              | 2   |                | 1   | 1              |     |                |     |              |     |

\*SCD—Severe coronary disease.

MCD—Minimal coronary disease.

## DISCUSSION

The prime purpose of this study was a survey of hypertensive heart failure in cases in which coronary arteriosclerosis was insignificant. The material with severe coronary disease served merely as controls. Nevertheless, no study of chronic congestive failure occurring in hypertension is complete without adequate consideration of the rôle of the coronary arteries.

Leyden<sup>8</sup> was among the first of modern clinicians to give a comprehensive description of the clinical and pathological aspects of acute and chronic coronary artery disease. Lisa<sup>9</sup> found that with the excep-

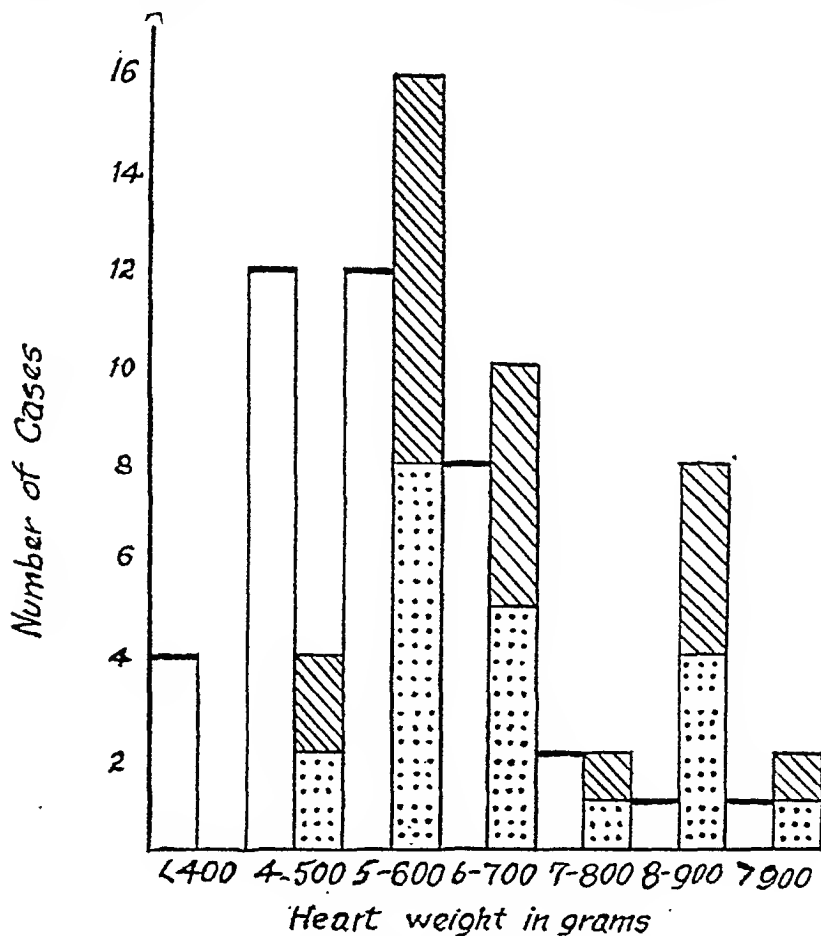


Fig. 4.—Showing tabulation of cases of major and minimal coronary arteriosclerosis against heart weight. This table indicates that the cases with minimal coronary arteriosclerosis had greater heart weights. Of the hearts of both groups weighing 500 gm. or more, 61 per cent had minimal coronary artery disease.

tion of very small scars, chiefly in the left ventricle and interventricular septum, the myocardium presented no marked gross changes in cases of hypertension without major coronary artery disease. Bell and Clawson,<sup>10</sup> in a study of 420 cases of essential hypertension, noted myocardial insufficiency in 187 instances and symptoms referable primarily to the coronary arteries in a group of 67 patients. Coronary sclerosis was more common and more severe in the hypertensive cases than in those of nonhypertensive heart disease. It is striking that in the hearts weighing 400 gm. or less, myocardial insufficiency was un-

common, while in those weighing 500 gm. or more, myocardial insufficiency was frequent. The average heart weight of those showing myocardial insufficiency was highest in their entire series and decidedly higher than in the group with coronary disease as the salient condition.

Clawson<sup>11</sup> studied 139 cases of hypertension in a survey of 429 cases of cardiac failure. Of these 139 patients the causes of death were: in 78, cardiac failure; in 37, coronary sclerosis; in 16, cerebral arteriosclerosis; and in 8, renal insufficiency. Among the 78 that died from congestive heart failure, there was no cellular proliferation or exudation in the myocardium except in those with infarcts. Severe coronary sclerosis was present in 15.5 per cent and severe myocardial fibrosis in only 2.5 per cent. Slight coronary sclerosis was present in 69 per cent and slight myocardial fibrosis was noted in 44.5 per cent. There was no narrowing of the coronary arteries in 15.5 per cent and no myocardial fibrosis in 52.5 per cent of the cases. Clawson was of the belief that myocardial fibrosis is of little importance in bringing about myocardial failure in hypertension, since myocardial fibrosis is common to patients with and without hypertension.

Christian,<sup>12</sup> in discussing the problem of hypertensive heart disease, also noted that the hypertrophy of the heart was the striking feature of the cases in failure, whereas many patients with symptomless hypertension had little or no cardiac hypertrophy. He raised the question of the rôle of anoxemia in congestive heart failure, for he believed that in cardiac hypertrophy the capillaries do not increase in number. Furthermore, when the capillaries become widely separated, there is a diminished supply of nutritive materials and oxygen and improper removal of metabolites. This conjecture was observed by us to be true.

Arteriolar counts in our material revealed an inverse relationship between the number of arterioles and heart weight. It is apparent that with an increase in width of the muscle fibers, the vessels would be called upon to supply an increased volume of myocardium in proportion to the degree of hypertrophy. The demand would be even greater in the presence of major coronary artery disease. This separation may also produce stretching of the vessel walls and a decrease in tortuosity which may be related to the dynamics of blood flow.

Averbuck,<sup>13</sup> after studying 40 cases, concluded that heart failure in hypertension was most commonly due to coronary sclerosis and thrombosis. Nemet and Gross,<sup>14</sup> however, in studying 100 cases of arteriosclerotic heart disease, found coronary vessel and muscle damage as common in patients without congestive heart failure as in those with congestive failure.

Nathanson,<sup>15</sup> in a series of 113 cases of coronary artery disease, observed congestive heart failure in but 6.6 per cent of those with normal sized hearts, while in the group with cardiac enlargement, congestive heart failure occurred in 63.2 per cent. It is striking that of the group in congestive heart failure, cardiac enlargement was

present in 93.4 per cent. It is evident that the distinguishing feature of our cases in failure as well as of those recorded in the literature is the presence of cardiac hypertrophy in those in failure and its infrequency in those not in failure.

Wiggers<sup>16</sup> stated that the volume of flow through coronary artery collateral vessels depends upon the magnitude of pressure differences. In slow occlusion, altered pressure gradients distend normally useless channels. At such times, the pressure gradients are favorable for the development of flow through coronary and extracoronary anastomoses. A flow from the ventricular cavity to the artery during systolic ejection may develop and a to-and-fro movement could occur during each heart cycle.

Since death in coronary disease does not usually occur after the first attack, both intracardiac and extracardiac collaterals may subsequently arise so that the circulation is actually improved. So far as the circulation itself is concerned, some factor besides coronary disease must be the cause of congestive heart failure, since, in the surviving heart, the blood supply is greater than at the time of thrombosis.

The rôle of myocardial fibrosis in cardiac hypertrophy has occupied the attention of many pathologists. Moenckeberg<sup>17</sup> quoted Goldenberg<sup>18</sup> who observed regularly in cardiac hypertrophy a spreading out of the connective tissue septa between the individual muscle fibers. This replacement fibrosis was found to be a variable process, and was greater in some areas than in others. Tangl<sup>13</sup> denied that cardiac hypertrophy was associated with myocardial fibrosis. Dehio,<sup>19</sup> however, observed in hypertrophied hearts, a diffuse increase in connective tissue which he called myofibrosis cordis. The fibrosis was in proportion to the extent and duration of the hypertrophy and failure. The degree of fibrosis was proportional to the dilatation of the heart chambers. It is, furthermore, noteworthy that Bell and Clawson,<sup>10</sup> Levine,<sup>20</sup> Lisa,<sup>9</sup> V. Levine,<sup>21</sup> and Plaut and Kramer<sup>22</sup> observed no correlation between vascular and muscular lesions.

Saphir<sup>23</sup> et al cited cases of myocardial infarcts without complete coronary obstruction and attributed infarction to temporary coronary insufficiency resulting in lowered arterial pressure so that the infarcted area temporarily is inadequately supplied with blood. Plaut and Kramer<sup>22</sup> mentioned anemia, collateral circulation, and other factors bearing on this relationship and reported a case of myocardial infarction associated solely with arteriolosclerosis. Dehio<sup>19</sup> felt then, as there is good reason to believe now, that a contributory cause to myofibrosis cordis is increased intracardiac diastolic blood pressure, due to cardiac dilatation, leading to capillary stasis and induration. In this manner, on purely dynamic grounds, it is possible to explain both patchy myocardial fibrosis and the independence of myocardial fibrosis from coronary disease. The small areas of fibrosis in the myocardium of hypertensive hearts appear to us to be concomitant with

or a by-product of the hypertrophied heart rather than a cause of heart failure. The danger of drawing too close a cause-and-effect relationship, even in the presence of coronary arteriosclerosis, is apparent.

It is well established that vascular spasm may play a significant rôle in clinical medicine. Ricker<sup>24</sup> observed that vascular segments form autonomous units with the vascular response dependent upon the strength of the stimulus. According to him, spasm may be followed by stasis and paralysis of a vascular segment. F. Lange<sup>25</sup> noted that weak stimuli produce vasodilatation and strong stimuli cause vasoconstriction. With very strong stimuli, constriction is followed by paralysis of the vessel wall. Vascular necrosis may follow dilatation and slowing of the circulation that has lasted for a long time. Lewis and Landis,<sup>26</sup> using ergot, made similar observations and produced necrosis of the cock's comb from circulatory stasis. In the stages of stasis or thrombosis, local arrest of the circulation and gangrene of the comb developed. The implications of the concept of arterial spasm for clinical medicine are far reaching and important in explaining the disparity between morbid physiology and morbid anatomy.

If the concept of vascular spasm is accepted, it is conceivable that an area of tissue supplied by a spastic vessel may undergo necrobiosis of varying degrees depending upon the severity and duration of the vascular reaction. This theory would explain the frequency of myocardial fibrosis observed by Neubuerger<sup>27</sup> in epileptics in the absence of corresponding vascular damage. Likewise, vascular spasm is compatible with the occurrence of sudden anginal seizures and the well-known cases of sudden death, in the absence of anatomical cause of death.

V. Levine<sup>21</sup> attributed significance to the rôle of vascular spasm since he could not find an organic basis for myocardial scarring in many of his cases of hypertensive heart failure. Jaffé and Bross<sup>28</sup> cite a case of sudden death, found at necropsy to have delicate coronary arteries and on histological examination, an acute myocardial exudate. They believed death was due to a functional vascular disturbance.

It is the experience of many pathologists that there is a lack of exact correlation between major coronary vessel disease and muscle damage. This disparity may be explained by mechanical or functional considerations. Cases have been recorded, and we have observed instances, of single or of even double coronary artery thrombosis without myocardial infarction. Furthermore, myocardial infarction without a corresponding coronary artery occlusion has also been reported. Some extracoronary, or even extracardiac factor or factors must play a rôle in the nutrition of the heart. Perhaps these factors also play a part in the aging of the heart and in providing nutrition to counteract advancing coronary arteriosclerosis.

Moritz, Hudson, and Orgain<sup>29</sup> established the existence of extra-cardiac anastomoses through pericardial adhesions. Beck and Tichy<sup>30</sup> observed that coronary thrombosis was better tolerated if a previous collateral circulation had been prepared. Wearn<sup>31, 32</sup> and his co-workers reported the existence of communications, the thebesian vessels, between the coronary arteries and veins and the chambers of the heart and that as much as 90 per cent of the arterial blood may escape through the thebesian vessels. Leary and Wearn<sup>33</sup> reached this conclusion from cases of occlusions of both coronary arteries without associated myocardial damage.

Kretz<sup>34</sup> was of the belief that the thebesian vessels account for the disproportion between morbid changes of the coronary arteries and cardiac function. He thought that despite marked coronary damage the heart may be fully capable of performing its work. In a case of tuberculous myocarditis with destruction of the large coronary arteries and veins, Bellet, Gouley, and McMillan<sup>35</sup> found the thebesian vessels dilated and connecting the myocardium with the remaining intramural veins. Bohning, Jochim, and Katz<sup>36</sup> believed the thebesian vessels may nourish the heart in pathological conditions. The rôle of the thebesian vessels, however, was denied by Robertson<sup>37</sup> who thought that vascular pericardial adhesions play a rôle in the nourishment of the heart. Batson and Bellet<sup>38</sup> were of the belief that reversal of flow in the coronary veins is another factor in the nourishment of the heart. The efficacy of this pathway was recently denied by Wiggers.<sup>16</sup>

In our material, an increase of sinusoids was observed in cardiac hypertrophy in some cases. In small hearts, despite coronary disease, however, they were either not increased or when increased, this increase was never more than minimal. Numerical analysis of the sinusoids reveals no exact correlation with either duration or severity of congestive heart failure, cardiac hypertrophy, or coronary disease. This is as is to be expected since an increase in sinusoids is but one of several possible mechanisms by which the circulation to the heart itself is maintained. The striking feature is, however, the noteworthy frequency with which this mechanism is brought into play in enlarged hearts.

The existence of these additional vascular channels accounts for the lack of correspondence between vascular and myocardial damage. These pathways may explain, further, why, with similar muscle and vessel damage, some hearts go into congestive heart failure sooner than others and why enormous hearts even with severe coronary disease resist congestive heart failure a long time. It is thus easily understandable why the anatomical examination of a heart yields no insight into its physiological activity during life.

*Cardiac Hypertrophy.*—It is a generally accepted physiological maxim that when a muscle is required to do increased work, it undergoes hypertrophy. As a corollary, it may be said that if a muscle is found

to be hypertrophied, the conclusion is justifiable that it has performed increased work. The human heart, by increase of its muscle mass, is also capable of doing more work. While the condition responsible for such increase in mass is a disease, muscle hypertrophy is merely a mechanical response to compensate for increased diastolic stretching. Cardiac hypertrophy similarly, in itself, is not a disease. In fact, the hypertrophied muscle is stronger than the ordinary to meet increased physiological demands. Failure of the mechanism responsible for cardiac hypertrophy, however, results in a decrease of contractile power. At such times, hypertrophy no longer occurs, despite the persistence of the cause responsible for hypertrophy.

Dilatation of the heart muscle, as in any other muscle, is in itself also not a sinister process. In fact, temporarily increased demands on the normal heart can only be met by increase in diastolic fiber length or fiber tension which is the physiological response to demand for increased work. Furthermore, without such increase in diastolic fiber length, its counterpart, cardiac hypertrophy, does not appear. When, however, for some unknown reason, dilatation ceases to produce the stimulus for hypertrophy and dilatation is progressive, the pernicious effects of dilatation alone are in evidence. At such times, increased fiber length is not associated with an increase in the height of the isometric muscle contraction curve. It follows, therefore, that dilatation, which is the means by which the heart hypertrophies and does more work, is also the mechanism by which cardiac insufficiency ultimately develops.

Cardiac enlargement is a cardinal feature in chronic congestive heart failure of all types, and is not limited to the hypertensive heart. Christian<sup>12</sup> has suggested that the mechanism of cardiac hypertrophy and failure may be the same in patients with and without valvular disease. In rheumatic heart disease, congestive heart failure is very frequently associated with active carditis, as shown by Rothschild, Kugel, and Gross.<sup>39</sup> However, in the cases not showing active carditis, we have noted the frequent incidence of marked cardiac hypertrophy. The insufficiency of the pulmonic circulation also has been shown by Fineberg and Wiggers<sup>40</sup> to be dependent upon fatigue of the right ventricle.

In syphilitic aortic insufficiency, too, congestive heart failure occurs practically always in massive hearts. Clawson and Bell<sup>41</sup> felt that in syphilitic heart disease, the most conspicuous change in the myocardium was hypertrophy, and that little attention need be paid to the gross or microscopic changes. In these cases congestive heart failure is not related to the state of the coronary arteries since they are often normal. Narrowing of the ostia of the coronary arteries is quite common, though the heart in failure is most commonly hypertrophied. It is thus seen that, excluding the cases in which congestive failure is due to an inflammatory or toxic process, the heart in failure

is, in the majority of instances, a hypertrophied heart. There is a common background for congestive heart failure of all types. The hypertensive heart in hypertrophy and failure appears to us to follow these common dynamic laws.

Increased diastolic length or tension is a significant, though not the sole, cause of cardiac hypertrophy. In severe anemia and in a considerable number of cases of essential hypertension, in which chronic increases of diastolic length may be assumed, hypertrophy does not develop. In extensive myocardial infarction, greater diastolic fiber stretching may also occur from primary loss of contractility. Though this type of case on physiological grounds could conceivably lead to cardiac hypertrophy, the production of increase in cardiac mass solely from coronary disease or myocardial infarction alone has not been substantiated clinically. Furthermore, despite primary loss of contractile power, congestive heart failure is uncommon in small hearts. The factor preventing hypertrophy in the exceptionally small heart in failure is unknown. Evidently, an additional factor must be present to produce increased cardiac mass. However, in the vast majority of cases without cardiac hypertrophy, congestive heart failure does not appear. The clinical implication of this fact is that even in the presence of major coronary artery disease, the hypertensive heart which is not greatly enlarged frequently does not go into failure.

*Anoxemia.*—Starling and Visscher<sup>42</sup> showed that the energy of contraction of a fiber is proportional to diastolic fiber length. Hemingway and Fee<sup>43</sup> observed a direct linear relationship between the diastolic volume and oxygen consumption. Evans and Matsuoka<sup>44</sup> stated that with a constant output, the work of the heart is proportional to, and increases up to, a maximum arterial pressure beyond which the heart fails. However, with low oxygen content, Jariseli and Wastl<sup>45</sup> noted cardiac dilatation, proportional, according to Van Liere,<sup>46</sup> to the degree of anoxemia. In other words, while oxygen consumption is proportional to diastolic length or dilatation, the dilated heart needs more oxygen to pump a given amount of blood.

In experimental tachycardia produced by mechanical means, and from hyperthyroidism, Menne, Jones, and Jones<sup>47</sup> observed a parallelism between the increased heart rate and the myocardial lesions. Buehner and von Lucadou<sup>48</sup> demonstrated disseminated necroses in animals exercised after bleeding and in animals not bled but severely strained. Rosin<sup>49</sup> showed marked fatty infiltration of the myocardium from diminished oxygen concentration. In chronic severe anemia in which anoxemia may be assumed, tigering and fatty infiltration occur.

Hill<sup>50</sup> demonstrated that the rate of diffusion of oxygen varies inversely as the square of the distance to be traversed or, in other words, according to the thickness of the muscle fibers. Harrison<sup>51</sup> observed that the pulse rate of different animals varies roughly inversely as the thickness of the heart muscle fiber. However, in the hypertrophied



human heart, the pulse rate is not correspondingly slow. Since the mean head of pressure or oxygen tension in the capillary is the same, the part of the fiber near a capillary will receive oxygen while the innermost part of the fiber will receive a diminished supply. Patterson and Starling<sup>52</sup> showed that for a given minute volume, the oxygen consumption was greater per beat, but less per minute at slow than at fast pulse rates. It follows that when the fiber is thicker than normal, with diastole not prolonged and the pulse rate not proportionately diminished, some degree of anoxemia of the heart muscle must sooner or later develop. Evidently, hypertrophy, a compensatory mechanism, has in it, if progressive, the danger of resulting, sooner or later, in cardiac fatigue. Further proof of this fact is that normal hearts go into failure from very rapid rates, whereas enlarged hearts go into failure much sooner from merely slightly augmented heart rates. The appearance of congestive heart failure under these circumstances is probably related to anoxemia. Furthermore, anoxemia would also account for the development of myocardial fibrosis with and without coronary sclerosis without being dependent upon the latter. It is plausible that myocardial fibrosis would be greater, however, in massive hearts as well as in hearts with coronary disease.

*Additional factors.*—It was shown by Elias and Feller<sup>53</sup> that a contractile mechanism is present in the liver veins which bears directly upon the state of filling and the stroke volume of the heart. Indeed, the circulation in the hepatic veins may actually come to a standstill from a dilated right auricle. This mechanism may be of great significance in maintaining the dynamics of circulatory efficiency. It was also shown by Mautner<sup>54</sup> and his associates that the opening and closure of the liver veins was governed by the vagus and sympathetic nerves and by the interchange of fluid in the liver. The contraction of the diaphragm and the resulting effects on the intrathoracic and intra-abdominal pressure and the filling of the heart is another important dynamic factor in the circulation.

*Metabolic factors.*—It is impossible to answer just when, and for that matter why, hypertrophy ceases to continue and the heart, despite the physiological stimulus of dilatation, fails to undergo further hypertrophy. The anatomical changes do not offer an adequate explanation of chronic congestive heart failure. The physiological facts merely indicate the dynamic conditions involved in cardiac hypertrophy. Consideration of the metabolic factors may therefore be of great value.

Seccof et al<sup>55</sup> showed differences in creatine content of the right and left ventricles. Cowan<sup>56</sup> demonstrated decreased creatine content in the hypertrophied heart muscle. This was more marked in cases showing congestive failure. A conspicuous increase in carbon dioxide and dextrose consumption during ventricular fibrillation as compared to the normally beating heart was shown experimentally by Hooker

and Kehar.<sup>57</sup> Following coronary occlusion in animals, the infarcted heart, according to Himwich, Goldfarb, and Nahum,<sup>58</sup> loses appreciable glycogen, which appears in part as increased carbohydrate and lactic acid. Long and Evans,<sup>59</sup> studying rats suffering from induced tetany, demonstrated marked reduction of the glycogen content of both the heart and the gastrocnemius muscle. Following reduction of oxygen, the cardiac glycogen fell markedly. Low cardiac glycogen stood in close relationship to cardiac failure while anoxic animals allowed to recover had marked rises of glycogen.

Herrmann, Decherd, and Schwab<sup>60</sup> confirmed the loss of creatine in heart failure and in experimental myocarditis and, in addition, a loss of glycogen in the infarcted rabbit and dog heart. Clark, Eggleston, and Eggleston<sup>61</sup> showed that the hydrolysis of phosphagen is the immediate source of the energy of the contraction of the heart. Phosphagen disappears faster from tortoise auricular strips deprived of oxygen if the heart is beating rhythmically than if it is quiescent. The demonstration by Cowan<sup>56</sup> of creatine diminution in cardiac hypertrophy which was greater in congestive heart failure lends credence to this attitude, and recently Herrmann and associates<sup>60</sup> have reported phosphocreatine disturbances in experimental congestive heart failure.

Since impairment of function of any tissue is on final analysis due to impaired exchange of oxygen and metabolites, these factors are also, on such final analysis, the cause of failure and replacement fibrosis in the human heart. This view is acceptable if by it we understand that insufficient oxygenation and lack of metabolites in hypertensive hearts are no more due solely to coronary disease than the failure of rheumatic or emphysema hearts is due solely to coronary disease.

On final analysis, it appears that the problem of myocardial failure in essential hypertension must resolve itself into the disturbed relationship between muscle fiber size and the volume of blood flow through the capillary bed.

Even in the presence of major coronary artery disease, the heart with fibers of normal thickness may be capable of a stroke volume of adequate contractility to maintain circulatory efficiency. Indeed, though these hearts show some diminution of cardiac reserve, chronic congestive heart failure occurs relatively uncommonly in the absence of additional factors, such as hypertension, tachycardia, toxemia, and anemia which may cause chronically increased diastolic length and tension. Failure occurs when hypertrophy ceases to develop despite increasing diastolic length. Anoxemia, at such times, or metabolic factors are probably the determining factors of congestive heart failure.

Coronary disease, per se, is rarely a sole cause of chronic congestive heart failure. In the presence of cardiac hypertrophy with minimal coronary arteriosclerosis, congestive heart failure does occur, even if

infrequently. The cases of failure with coronary disease show, in the overwhelming majority, varying but very considerable hypertrophy. In our material, the patients with severe coronary disease and failure did not show hypertrophy as massive as those in which coronary disease was minimal. Failure in those with severe coronary disease, when present, commonly did not exceed two years. The failure in many was more or less acute following sudden impairment of nutrition as by an additional coronary occlusion. Under such circumstances, primary loss of contractility does not result in preponderant additional cardiac hypertrophy, and congestive heart failure supervenes.

In the group with minimal coronary disease, however, despite the larger size of fiber, greater diastolic fiber length for a long time constitutes an adequate stimulus for additional cardiac hypertrophy. Apparently, an adequate vascular supply keeps pace with the increasing muscle mass. This is shown by the fact that the hearts with minimal coronary disease lived longer in congestive heart failure and their heart weights were greater than those of the cases with major coronary artery disease. Congestive heart failure in both types is, however, the end-result of the hypertrophied heart which is unable to undergo further hypertrophy. The hypertrophied fiber may, however, for a long time, work at optimum efficiency despite diminished vascularity. In an enormous heart with the individual fiber greatly stretched and thickened and the blood supply relatively and absolutely diminished, an additional impairment of nutrition such as a small vascular lesion, which in normal sized heart may produce no symptoms, may, in the massive heart, produce acute or terminal congestive heart failure.

Any factor interfering with the nutrition of the muscle fiber, be this primary as in an infection or toxemia, or secondary from anoxemia as in hypertrophy, severe coronary artery disease, anemia, or tachycardia, will impair the contractility of the muscle fiber. Such loss of contractility may produce acute and chronic congestive heart failure. In the disturbed metabolism of the individual muscle fiber, however, lies the ultimate cause of congestive heart failure.

#### SUMMARY

1. Cardiac hypertrophy is the feature common to cases of congestive heart failure irrespective of the presence or absence of major coronary artery disease. The congestive heart failure associated with an inflammatory or toxic cardiac lesion is an exception to this rule.

2. In hypertrophied heart muscle, the development of surface irregularities of the muscle fibers and alterations in the nuclei appear to be a compensatory mechanism to increase the diffusing surfaces.

3. A decrease in capillary and arteriolar tree proportional to the volume of the muscle mass was observed.

4. Three types of muscle changes were observed in many cases:
  - a. Microscopic acute infarcts similar to those seen in major coronary occlusion.
  - b. A slow process of fiber dissolution or fatty degeneration.
  - c. Connective tissue replacement of myofibrillae by an insensible merging of the muscle fibers with connective tissue.

5. Anatomical, functional, and mechanical factors appear to play a rôle in myocardial fibrosis. This fibrosis is not directly dependent upon coronary sclerosis even in the presence of marked coronary disease. However, myocardial fibrosis appears to be related to anoxemia from whatever cause.

6. A collateral circulation, both intracardiac and extracardiac may play a rôle in preventing failure of the hypertrophied heart. Sinusoids were found to be increased in number and size in many hypertrophied hearts and under certain circumstances are probably intimately associated with the nourishment of the heart.

7. Congestive heart failure is due to coronary insufficiency only in the sense that impairment of nutrition and necrobiosis are, on final analysis, a function of blood supply in heart tissue as in any other tissue.

8. Congestive heart failure is the failure of the heart which fails to undergo further hypertrophy. The cause of failure lies in some disturbance other than the anatomical, though cardiac hypertrophy is the cardinal associated finding. Such hearts may be correlated with demonstrable metabolic disturbances which appear to be the ultimate cause of failure.

#### ILLUSTRATIVE CASES

CASE 1.—No. 24032. A man, sixty years of age, a known diabetic for fifteen years; with coldness and blueness of the feet for five years and anginal seizures of two years' duration. Four months before admission, he developed an ulcer over the left heel. Three months later, an ulcer appeared on the posterior aspect of the left foot. Examination showed advanced peripheral arteriosclerosis, gangrene of the left third toe, and an ulcer of the left heel. After two months in the hospital, he was discharged improved. However, after being home several days, an ulcer appeared in the lateral aspect of the right heel and another on the second right toe and he was readmitted. Three weeks after his admission, he developed sharp precordial pain and dyspnea at rest and several days later, pulmonary congestion and peripheral edema, and he died suddenly.

Necropsy showed a heart weighing 510 gm., marked coronary arteriosclerosis, marked narrowing of the right coronary artery by a recent thrombus and severe stenosis of the left coronary, and partial occlusion of the anterior descending branch of the left coronary artery, fibrosis of the interventricular septum and apex of the left ventricle, and recent infarction of the posterior wall of the left ventricle. Microscopically, there was slight, but definite increase of sinusoids.

This case illustrates the fact that despite severe coronary arteriosclerosis and myocardial damage in a large heart, congestive heart failure may not occur till the advent of an additional burden, such as recent muscle or vessel damage.

CASE 2.—No. 21286. A man, seventy-three years of age, with a history of weakness of several years' duration, dyspnea, and precordial pain of one year's duration and paroxysmal nocturnal dyspnea of ten months' duration. Examination showed minimal congestive heart failure with hepatic and pulmonary congestion and slight ankle edema four months before death.

Neeropsy showed a heart weighing 380 gm. and no cardiac hypertrophy. The coronary arteries were pipestem with reduction of the lumens of the left circumflex branch, occlusion of the left anterior descending branch and narrowing of the right coronary artery. There was an infarct at the apex of the left ventricle and marked fibrosis of the interventricular septum and right ventricle. Microscopic examination showed numerous sinusoids in the myocardium.

This case shows (1) the relatively uncommon development of congestive heart failure in the absence of cardiac hypertrophy, (2) the late and mild failure in a small heart despite extensive coronary disease, (3) the rôle of the sinusoids in nourishing the heart itself, and (4) that coronary disease per se does not cause cardiac hypertrophy.

CASE 3.—No. 11358R. A female, sixty-two years of age, was observed at Montefiore Hospital over a period of three years, with a history of edema of the legs and abdomen of four years' duration and progressive dyspnea on exertion, of three and one-half years' duration. The blood pressure was 218 systolic and 128 diastolic. The liver edge was felt four fingers below the costal margin; cardiac asthma appeared. A left hemiplegia developed which in part improved. She was admitted to the hospital nine times on account of myocardial insufficiency, headaches, epistaxis, nausea, and epigastric pain. She developed acute appendicitis two days before death, and died of peritonitis. The signs of congestive heart failure were minimal before death.

At neeropsy, she was found to have generalized peritonitis. The heart weighed 750 gm. The orifices of the coronary arteries were slightly encroached upon by atheromatous plaques. The coronary arteries were thin and soft. There was a moderate number of minute microscopic scars. The sinusoids showed a moderate to marked increase.

This case indicates the long duration of congestive heart failure in a very large heart in the absence of major coronary artery disease. The microscopic scars may be attributed to anoxemia. The numerous sinusoids may have played a rôle in nourishing the heart and preventing additional cardiac insufficiency.

CASE 4.—No. 21791. A male forty-three years of age, with hypertension, known one year, dyspnea and choking on exertion, of fourteen months' duration, and multiple cerebral vascular insults. Death was due to a cerebral insult. There was no history of congestive heart failure.

Neeropsy showed a heart weighing 550 gm., marked atheromatosis of the left anterior descending and transverse coronary arteries with marked reduction of the lumens, marked atheromatosis of the right coronary artery with an old occlusion and a fresh mural thrombus with partial occlusion, and a small scar in the posterior wall of the left ventricle. There were numerous microscopic scars and only slight increase of sinusoids.

This case is indicative of the fact that despite severe coronary artery disease in a large heart, congestive heart failure need not appear even in the presence of a fresh mural thrombus in the right coronary artery.

## REFERENCES

1. Aschoff, L., and Tawara, S.: Die Heutige Lehre v. d. path. anat. Grundlage d. Herzschwäche, Jena, 1906, Gustav Fischer.
2. Karsner, H. T., Saphir, O., and Todd, T. W.: Cardiac Muscle in Hypertrophy and Atrophy, *Am. J. Path.* 1: 351, 1925.
3. Tangl, F.: Ueber die Herzhypertrophie u. das Physiologische Wachstum des Herzens, *Virchows Arch. f. path. Anat.* 116: 432, 1889.
4. Cohn, A. E.: Cardiac Muscle, *Special Cytology*, New York, 1928, Vol. 2, Paul B. Hoeber, Inc., p. 805.
5. Collier, W. D.: Adaptive Changes of Heart Muscle, *J. M. Research* 43: 207, 1922.
6. Wearn, J. T.: The Extent of the Capillary Bed of the Heart, *J. Exper. Med.* 47: 273, 1928.
7. Shipley, R. A., Shipley, L. J., and Wearn, J. T.: The Capillary Supply in Normal and Hypertrophied Hearts of Rabbits, *J. Exper. Med.* 65: 29, 1937.
8. Leyden, E.: Ueber die Sklerose der Coronar-Arterien und die davon abhängigen krankheitszustände, *Ztschr. f. klin. Med.* 7: 459 and 539, 1884.
9. Lisa, J. R.: The Decompensated Hypertensive Heart, *J. Lab. & Clin. Med.* 17: 211, 1931-32.
10. Bell, E. T., and Clawson, B. J.: Primary Essential Hypertension, *Arch. Path.* 5: 938, 1928.
11. Clawson, B. J.: Myocarditis, *AM. HEART J.* 4: 1, 1928.
12. Christian, H. A.: Speculations on Some Problems of Cardiac Failure, *South. M. J.* 20: 28, 1927.
13. Averbuck, S. H.: Heart Failure in Hypertension, *AM. HEART J.* 11: 99, 1936.
14. Nemet, G., and Gross, H.: The Interrelationship of Arteriosclerotic Heart Disease and Chronic Congestive Failure, *AM. HEART J.* 10: 643, 1935.
15. Nathanson, M. H.: Diseases of the Coronary Arteries, *Am. J. M. Sc.* 170: 250, 1925.
16. Wiggers, C. J.: Inadequacy of Normal Collateral Coronary Circulation and Dynamic Factors Concerned in Its Development During Slow Coronary Occlusion, *AM. HEART J.* 11: 641, 1936.
17. Moenckeberg, J. G.: in Henke-Lubarsch—Die Erkrankungen d. Myocards, *Handb. d. Spez. Path. Anat. u. Histol.* 2: Berlin, 1924, Julius Springer.
18. Goldenberg: quoted by Moenckeberg.
19. Dehio: quoted by Moenckeberg.
20. Levine, S. A.: Coronary Thrombosis, Baltimore, 1929, Williams & Wilkins Company.
21. Levine, V.: Myocardial Changes in Hypertension, *Arch. Path.* 18: 331, 1934.
22. Plaut, A., and Kramer, M. L.: Arteriolar Disease of the Heart, *Arch. Path.* 22: 393, 1936.
23. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes, *AM. HEART J.* 10: 567, 1935.
24. Ricker, G.: Pathologie als Naturwissenschaft-Relationspathologie, Berlin, 1924, Julius Springer.
25. Lange, F.: Studien zur Pathologie der Arterien, insbesondere zur Lehre von der Arteriosklerose, *Virchows Arch. f. path. Anat.* 248: 463, 1924.
26. Lewis, T., and Landis, E. M.: The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot, *Clin. Sc.* 2: 43, 1935.
27. Neuburger, K.: Herz, Epilepsie, Angina Pectoris, *Klin. Wchnschr.* 12: 1355, 1933.
28. Jaffé, R., and Bross, K.: Histologische Befunde bei Herzrupturen, *Centralbl. f. allg. Path. u. path. Anat.* 56: 246, 1932-33.
29. Moritz, A. R., Hudson, C. L., and Orgain, E. S.: Augmentation of the Extracardiac Anastomoses of the Coronary Arteries Through Pericardial Adhesions, *J. Exper. Med.* 56: 927, 1932.
30. Beck, C., and Tichy, V. L.: The Production of a Collateral Circulation in the Heart, *AM. HEART J.* 10: 849, 1935.
31. Wearn, J. T., Mettier, S. R., Klumpp, T. G., and Zschesche, L. J.: The Nature of Vascular Communications Between the Coronary Arteries and the Chambers of the Heart, *AM. HEART J.* 9: 143, 1933.
32. Wearn, J. T.: The Role of the Thebesian Vessels in the Circulation of the Heart, *J. Exper. Med.* 47: 293, 1928.
33. Leary, T., and Wearn, J. T.: Two Cases of Complete Occlusion of Both Coronary Orifices, *AM. HEART J.* 5: 412, 1929.

34. Kretz, J.: Ueber die Bedeutung der Venae Minimae Thebesii fuer die Blutversorgung d. Herzmuskels, *Virchows Arch. f. path. Anat.* 266: 647, 1927.
35. Bellet, S., Gouley, B. A., and McMillan, T. M.: Nourishment of the Heart Through Thebesian Vessels, *Arch. Int. Med.* 51: 112, 1933.
36. Bohning, A., Jochim, K., and Katz, L. N.: Thebesian Vessels in Nourishment of Myocardium, *Am. J. Physiol.* 106: 183, 1933.
37. Robertson, H. F.: The Reestablishment of Cardiac Circulation During Progressive Coronary Occlusion, *AM. HEART J.* 10: 533, 1935.
38. Batson, O. V., and Bellet, S.: The Reversal of Flow in the Cardiac Veins, *AM. HEART J.* 6: 206, 1930.
39. Rothschild, M. A., Kugel, M. A., and Gross, L.: Incidence and Significance of Active Infection in Cases of Rheumatic Cardiovalvular Disease During Various Age Periods, Clinical and Pathological Study, *AM. HEART J.* 9: 586, 1934.
40. Fineberg, M. H., and Wiggers, C.: Compensation and Failure of Right Ventricle, *AM. HEART J.* 11: 255, 1936.
41. Clawson, B. J., and Bell, E. T.: The Heart in Syphilitic Aortitis, *Arch. Path.* 4: 922, 1927.
42. Starling, E. H., and Visscher, M. B.: The Regulation of the Energy Output of the Heart, *J. Physiol.* 62: 243, 1926-27.
43. Hemingway, A., and Fee, A. R.: The Relationship Between the Volume of the Heart and Its Oxygen Usage, *J. Physiol.* 63: 299, 1927.
44. Evans, C. L., and Matsuoka, Y.: The Effects of Various Mechanical Conditions on the Gaseous Metabolism and Efficiency of the Mammalian Heart, *J. Physiol.* 49: 378, 1914-15.
45. Jarisch, A., and Wastl, H.: Observations on the Effect of Anoxemia Upon Heart and Circulation, *J. Physiol.* 61: 583, 1926.
46. Van Liere, E. J.: The Effect of Anoxemia on the Size of the Heart as Studied by the X-ray, *Am. J. Physiol.* 82: 727, 1927.
47. Menne, F. R., Jones, O. R., and Jones, N. W.: Changes in the Myocardium of Rabbits From Augmenting the Heart Rate Mechanically and From Induced Hyperthyroidism, *Arch. Path.* 17: 233, 1934.
48. Buechner, F., and von Lucadou, W.: Elektrokardiographische Veraenderungen u. disseminierte Nekrosen d. Herzmuskels bei experimenteller Coronarinsuffizienz, *Beitr. z. path. Anat. u. z. allg. Path.* 93: 169, 1934.
49. Rosin, A.: Morphologische Organveraenderungen beim Leben unter Luftverduennung, *Beitr. z. path. Anat. u. z. allg. Path.* 80: 622, 1928.
50. Hill, A. V.: Diffusion of Oxygen and Lactic Acid Through the Tissues, *Proc. Roy. Soc. London, Series B*, 41: 104, 1929.
51. Harrison, T. R.: *Failure of the Circulation*, Baltimore, 1935, Williams & Wilkins Company.
52. Patterson, S. W., and Starling, E. H.: On the Mechanical Factors Which Determine the Output of the Ventricle, *J. Physiol.* 48: 356, 1914.
53. Elias, H., and Feller, A.: *Stauungstypen bei Kreislaufstoerungen*, Berlin, 1926, Julius Springer.
54. Mautner, H.: Die Innervation der Venensperre in der Leber, *Monatschr. f. Kinderh.* 27: 385, 1923-24.
55. Seecof, D. P., Linegar, C. R., and Myers, V. C.: Difference in Creatine Concentration of Right and Left Ventricular Cardiac Muscles, *Arch. Int. Med.* 53: 574, 1934.
56. Cowan, D. W.: The Creatine Content of Normal and Abnormal Human Hearts, *AM. HEART J.* 9: 378, 1934.
57. Hooker, D. R., and Kehar, N. D.: Carbohydrate Metabolism of the Heart During Ventricular Fibrillation, *Am. J. Physiol.* 105: 246, 1933.
58. Himwich, H. E., Goldfarb, W., and Nahum, L. H.: Changes of the Carbohydrate Metabolism Following Coronary Occlusion, *Am. J. Physiol.* 109: 403, 1934.
59. Long, C. N. H., and Evans, G. T.: Glycogen Content of the Rat Heart, *Proc. Soc. Exper. Biol. & Med.* 30: 186, 1932-33.
60. Herrmann, G., Decherd, G. M., Jr., and Schwab, E. H.: Some Biochemical Factors in Heart Failure, *South. M. J.* 29: 386, 1936.
61. Clark, A. J., Eggleton, M. G., and Eggleton, P.: Phosphagen in the Perfused Heart of Frogs, *J. Physiol.* 75: 332, 1932.

# AURICULAR PAROXYSMAL TACHYCARDIA (POSSIBLY NOMOTOPIC) WITH VARIABLE AURICULOVENTRICULAR CONDUCTION TIME

STUDY OF A CASE OF EXCEPTIONAL DURATION WITH GRADUAL SLOWING  
OF THE HEART RATE\*

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AURICULAR paroxysmal tachycardia, although a very frequent disorder, presents few opportunities for cardiographic study, since many patients learn how to stop the seizures before distress or congestive changes appear. In any case, few attacks last sufficiently long to allow arrangements to be made for the taking of cardiographic records. Only four such tracings were obtained in a series of 1,200 cardiograms taken in our department over a period of four years. Paul White<sup>1</sup> has reported a series of 132 cases (82 females and 50 males); two-thirds showed no evidence of heart disease. He agrees, however, that the frequency of the condition is inaccurately represented in any statistical studies available at present. Lewis<sup>2</sup> classical tracings illustrate the commencement and termination of short paroxysms or bursts of extrasystoles, analogous to those which appear before and after the attack.

The abruptness with which the tachycardia begins and ends is generally considered as a characteristic feature of the condition. Indeed, such a history is often the only means of differentiation from attacks of palpitation resulting from undue heart consciousness, not necessarily associated with great increase of the heart rate. When the patient is seen during an attack, suspicion of the presence of this type of disorder, or of auricular flutter, is aroused by a heart rate of 140 per minute or more, which fails to respond to rest in the recumbent posture for an adequate period, and where constitutional disorders, such as hyperthyroidism, toxemia, or anemia, can be definitely excluded. Cardiographically, a high degree of regularity is apparent, the auricular complex is distorted in form, but the ventricular component is usually unaltered.

An opportunity recently presented itself whereby we were enabled to study at leisure an attack of paroxysmal tachycardia of supra-ventricular origin which departed from the classical description as regards the duration of the attack, and the regularity and mode of its

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Part of the work undertaken during the tenure of the Marion Clare Reddall Scholarship, University of Sydney.

1 Much abridged by Paul D. White, Boston. For further details, consult the author.



termination, but which presented the usual features of the condition in respect of the cardiographic findings, the sudden mode of onset of the paroxysms, and the secondary effects upon the circulation.

#### CASE REPORT

The patient, V. L., a female, aged thirty-nine years, visited the hospital because of a smothered feeling on waking at night, and sharp pain in the precordium and the left arm. She gave a history of having been breathless for several days, and for three days she had been unable to lie down on this account. She stated further, that from time to time during this period there had been violent throbbing of the heart, at times so marked that she was unable to read the newspaper held before her. She always had a florid complexion although this had never been of a bluish hue until seven weeks previous. Her health had been remarkably good and free from any evidence of rheumatism. Her mother had died at sixty years of age from "heart trouble."

The first attack of the present nature had been experienced seventeen years before, when her eldest child was eighteen months old. Since then she had had many short attacks, the longest interval between them being five years. The space of two years had separated several others. In each instance she described the onset as being sudden but could not be as definite about the mode of cessation. Her weight had increased considerably during the twelve months prior to her present attack and she stated that she had been more short of breath since then.

On examination, she weighed 155 pounds; presented a full round countenance with obvious purplish cyanosis of the cheeks and lips; this blueness was less marked in the case of the extremities. No edema was detected. She talked and carried on her usual activities without distress, but cyanosis deepened perceptibly as soon as she assumed the recumbent position. Movement of considerable amplitude could be observed in the cervical veins on each side, but there was no obvious venous distention elsewhere. She had a few carious teeth. No other focal infection was detected.

Examination of the precordium revealed a diffuse pulsation of large amplitude, maximal at a point in the anterior axillary line 15 centimeters from the midsternum at the level of the 4th intercostal space. No vibrations were palpable. The apical sounds were loud, completely irregular, sharp and slapping in quality, with relative emphasis on the second sound. At the base this exaggeration was less definite, and a soft systolic murmur was audible at the pulmonary area, varying with respiration. No congestive features were apparent in the examination of the respiratory, renal, or abdominal systems. The liver edge was impalpable. The patient was diagnosed as suffering from auricular fibrillation and recommended for admission. She was not anxious to leave her home, however, and continued to attend as an out-patient for seven weeks. On all occasions after the first visit, she presented a similar appearance and was mildly distressed, but the pulse rate was now entirely regular, varying between 150 and 160, and the heart sounds had a tick-tack quality. Pulsus alternans was present and the blood pressure readings averaged, systolic, 150; diastolic, 110 millimeters of mercury.

After seven weeks' attendance at the out-patient department, showing tachycardia at each visit, she consented to enter hospital for closer observation (Aug. 25, 1935). Symptoms and signs were as previously noted. Observations were made on her blood to exclude an erythremia, with the following results: red blood cells, 4,720,000 per cubic millimeter; hemoglobin, 14.4 gm. per cent, 90 per cent normal; mean corpuscular vol., 72 cubic microns; mean corpuscular hemoglobin,  $30 \times 10^{-12}$  gm.; mean corpuscular hemoglobin concentration, 43 per cent; color index, 0.9; white cells 9,500 per cubic millimeter.

*Other Findings.*—Level of fasting blood sugar, 79 milligrams per cent; degree of arterial oxygen saturation (Haldane method), 59 per cent; CO<sub>2</sub> combining power

of venous blood, 51 vols.; basal metabolism rate, plus 8 per cent; Wassermann and Kline tests, negative; temperature, normal except for one slight rise (to 100° F.) on the second day of the hospital stay.

A radiogram of the skull was normal. Attention was drawn to the unusual thickness of the cranial walls. A small degree of apical sepsis was present around two teeth.

The record of the changes in the diameters of the heart (as shown in teleradiograms) indicated progressive shrinkage in the transverse diameter of the organ especially affecting the right side, coincident with slowing of the heart rate. The pulse rate was recorded hourly, and revealed a marked fall in frequency during the hours of sleep, but never reaching below 90, while the maximum rate recorded during the waking hours was 160. After thirty-six days in bed the pulse rate had fallen to 80, where it remained in spite of increasing exercise, until the discharge of the patient from the hospital.

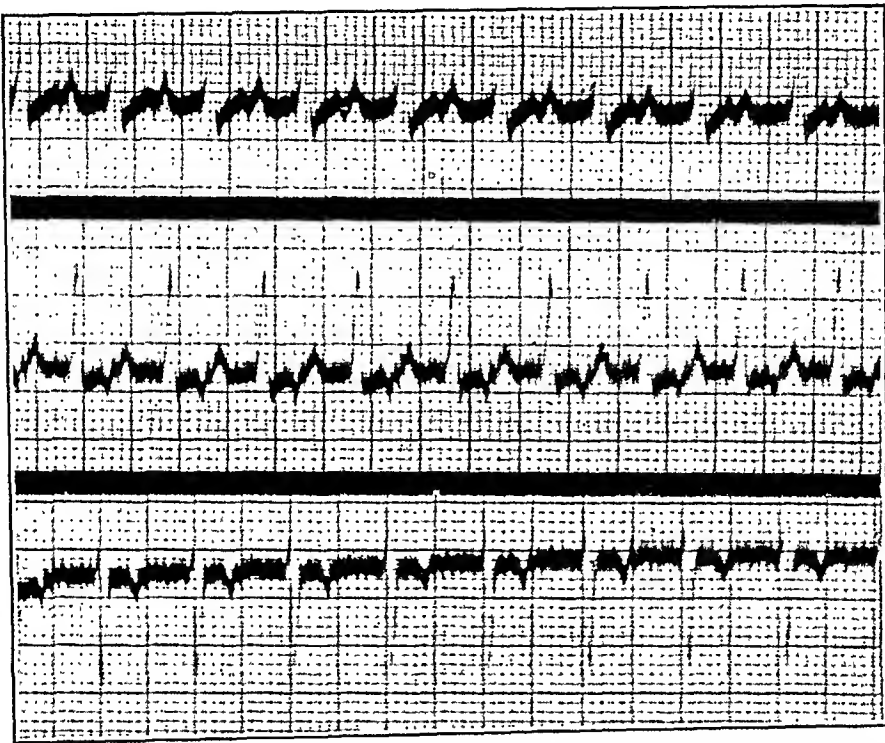


Fig. 1.—Initial tracing. All leads shown. The wave bears a distinct resemblance to that of nodal paroxysmal tachycardia, with a retrograde P-wave notching the upstroke of the T-wave. It was shown later, however, that the T-wave of Leads I and II is completely obscured by a bifid, aberrant, P-wave.

Reexamined on various occasions subsequently, the heart rate was consistently below 100 and the patient had experienced no further symptoms. The extraction of infected teeth, and an operation upon a septic thumb have since proved to be stimuli inadequate to initiate a further paroxysm.

Three months afterward (Dec. 23, 1935) the patient was sent for in the course of a routine follow-up. She arrived with a pulse rate of 168. She stated that she felt perfectly well. She had not been working hard, but had had a number of furuncles. No undue pulsation could be seen in the neck. The cardiogram showed sino-auricular tachycardia, in which no P-wave inversion appeared. The pulse slowed quickly on right carotid sinus pressure but no effect followed stimulation of the left carotid sinus.

#### CARDIOGRAPHIC ANALYSIS

In all, some 30 cardiograms were obtained during a period of two months. The first curve, obtained on July 30, 1935 (Fig. 1), was

originally interpreted as showing nodal tachycardia with the auricular complex notching the T-wave of the same QRS complex, and the R-P interval measuring 0.16 sec. Dr. J. Crighton Bramwell, who saw this patient and tracing, agreed with a probable diagnosis of nodal tachycardia. Three days later, with the heart beating regularly at the same rate, i.e. 160, prolonged pressure was applied to the right carotid sinus. The presumed retrograde P-wave, hereafter called P', was still visible (Fig. 2), but the curve as a whole was so flattened as to render further characteristics indistinguishable. The effect of this sinus stimulation was to render the pulse slightly slower and very irregular, with intermission of every third beat, the average time interval between the

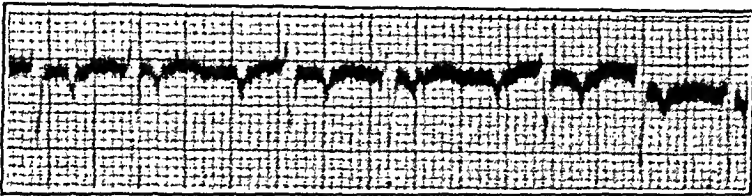


Fig. 2.—Lead III. Appearance on right carotid sinus pressure. Note regular appearance of bifid, aberrant, auricular complex, with single dropped beats at every third cycle.

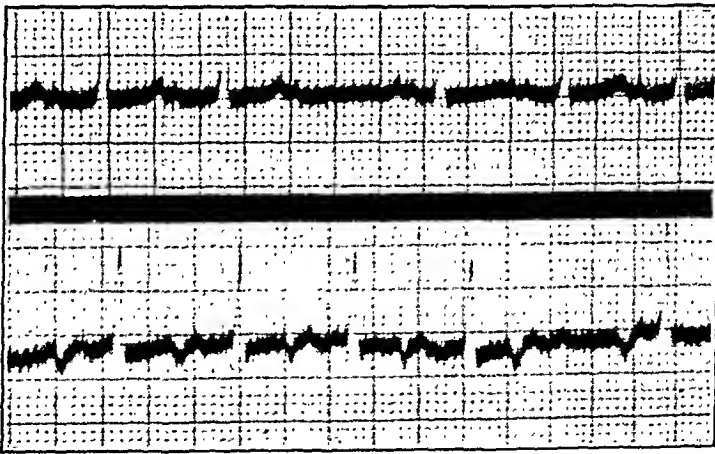


Fig. 3.—Leads I and II. Forty-five minutes after intravenous injection of digoxin 0.5 mg. Heart rate 120 per minute; conduction time progressively increased to 0.26 second just before a single missed beat occurs. The apparent T-wave in Lead I is then seen to be really a part of the deformed bifid auricular complex.

coupled beats being 0.48 sec. The groups of coupled beats were separated by a time interval of 0.72 sec. from each other in a remarkably constant manner.

The effect upon the cardiogram of intravenous injection of digoxin 0.5 mg. was next observed at intervals of 5, 15, 30, 45, and 60 minutes and compared with a cardiogram done immediately beforehand in which the heart rate was 150 per minute. Five minutes after the administration no changes were observable. Fifteen minutes later the pulse rate was 144 per minute. After thirty minutes the rate had decreased to 120. The P-waves of the second lead were still depressed. After forty-five minutes (Fig. 3) an interesting change had occurred;

the P' had altered its form, the first upstroke being higher than the second instead of the reverse as previously, the curve almost resembling a simple tachycardia. What at first had looked like a T-wave, however, appeared even after a missed ventricular complex and hence must be part of the auricular wave. The P-R interval had increased progressively from 0.2 to 0.28 sec. at which point a ventricular complex was missing. The resulting long pauses were of consistent length throughout the cardiogram. One hour later a similar phenomenon was observable. P<sub>2</sub> had a duration of 0.12 sec., and like P<sub>3</sub>, was inverted.

On Aug. 12, 1935, the patient, after half an hour's rest in the recumbent position, had a regular pulse rate of 56 per minute, but cardiographic analysis showed a 3:1 block and a conduction time of 0.2 sec. (Fig. 4). In this tracing it was possible to observe the exact character of the aberrant P-wave apart from any possible influence

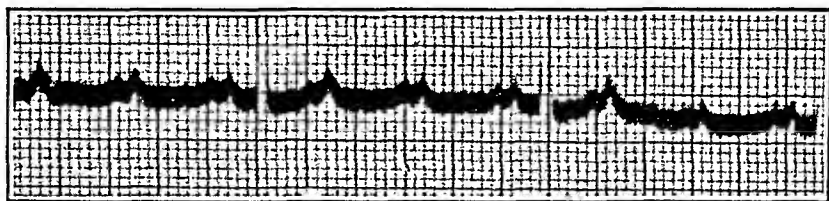


Fig. 4.—Lead I, with patient recumbent on Aug. 12, 1935, showing pulse rate of 56 due to 3:1 auriculoventricular block. The characters of the aberrant P-waves are here seen apart from any possible interference with T-waves. The influence of the latter deflection is to render the second peak of the P-wave higher than the first. It is on such appearances that all possibilities of a nodal tachycardia can be refuted.

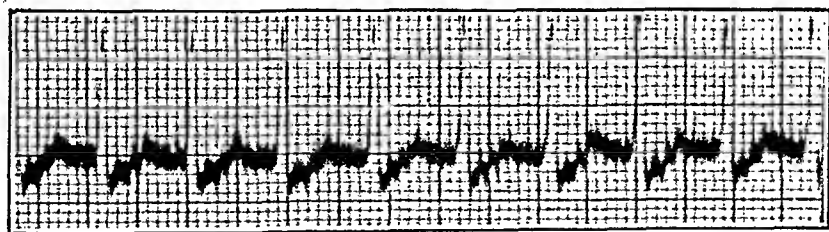


Fig. 5.—Lead II. Following exercise. Rate 170. There is no shortening of conduction time, so that the serrated auricular complex occurs immediately after the downstroke of the preceding S-wave.

upon it of the T-wave of a preceding ventricular complex. Its bifid form was preserved, and finally demonstrated that the apparent notching of T-waves which at first suggested nodal tachycardia, was illusory, and was due simply to the first deflection of the deformed auricular complex. On exercise the pulse rate rose suddenly to 168 while the conduction time remained 0.2 to 0.22 sec. (Fig. 5). Carotid pressure was then reapplied and the pulse became irregular with coupling. On release of the pressure the pulse again became regular with a 2:1 block. The effect of one gram of acetylcholine injected intravenously was studied at this juncture. The effect of this drug was to restore the rhythm of the pulse to a rate of 156 per minute.

With the patient sleeping under the influence of paraldehyde, and the pulse at 132, the conduction time was consistent in all leads, measuring 0.16 sec. The T-waves were flat throughout the whole of the

tracing. The absence of any intermission of the QRS complex, and the constancy and normal duration (0.16 sec.) of the conduction time are noteworthy features of these tracings taken during sleep.

By Sept. 20, 1935, the pulse had reached 96 per minute and it was now possible to see the P-wave separated by a distance of 0.24 sec. from the preceding T-wave (Fig. 6). The P-wave still maintained its bifid character in Lead I; was diphasic in Lead II, and inverted in Lead III. All S-T segments were depressed 1 to 2 mm. below the isoelectric level and marked left sided preponderance was present. Conduction time was now approximately 0.16 sec. Poorly marked T-waves were seen for the first time which were upright in Leads I and II, while no such waves were visible in Lead III. *In spite of what may be termed the cessation of the attack the abnormal features of the P-wave in all leads were maintained.* It is of interest that

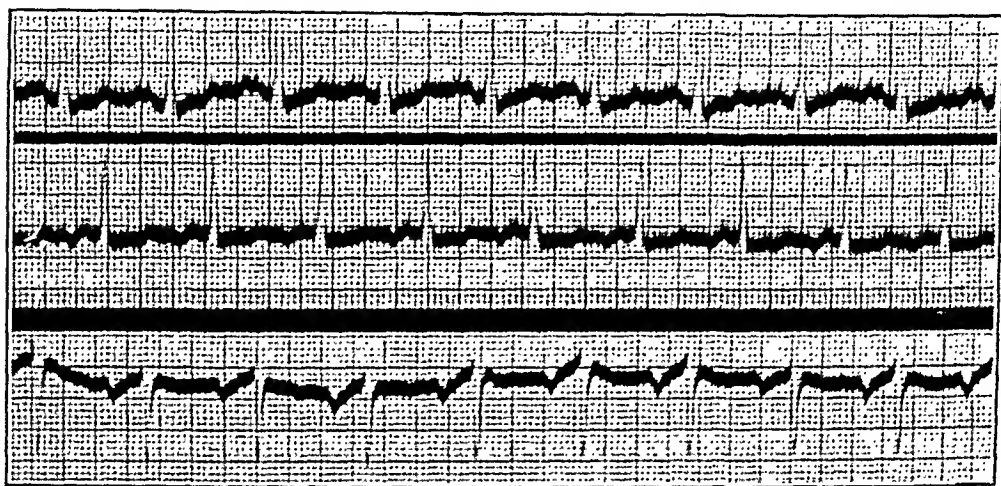


Fig. 6.—Leads I, II, and III soon after fall of pulse rate to normal. Observe character of auricular complexes, still retaining somewhat the same form as during the paroxysm. Conduction time 0.2 second.

attempts to abolish the disturbance of rhythm in this case by quinine, quinidine, digitalis, acetylcholine, adrenalin, and atropine were all equally fruitless.

#### DISCUSSION

This patient presents several departures from the classical description and usual criteria of auricular paroxysmal tachycardia. Even the question of nomenclature may be disputed. The patient, however, has had repeated attacks of tachycardia of a paroxysmal nature. They are not ventricular in type. At first the cardiogram was considered to represent a seizure of auriculoventricular nodal origin. The appearance of an aberrant P-wave in positions isolated from any ventricular deflections, and the absence of nodal extrasystoles immediately after the attack, throw reasonable doubt upon a genesis of ectopic impulse in the auriculoventricular node itself or its immediate neighborhood. The

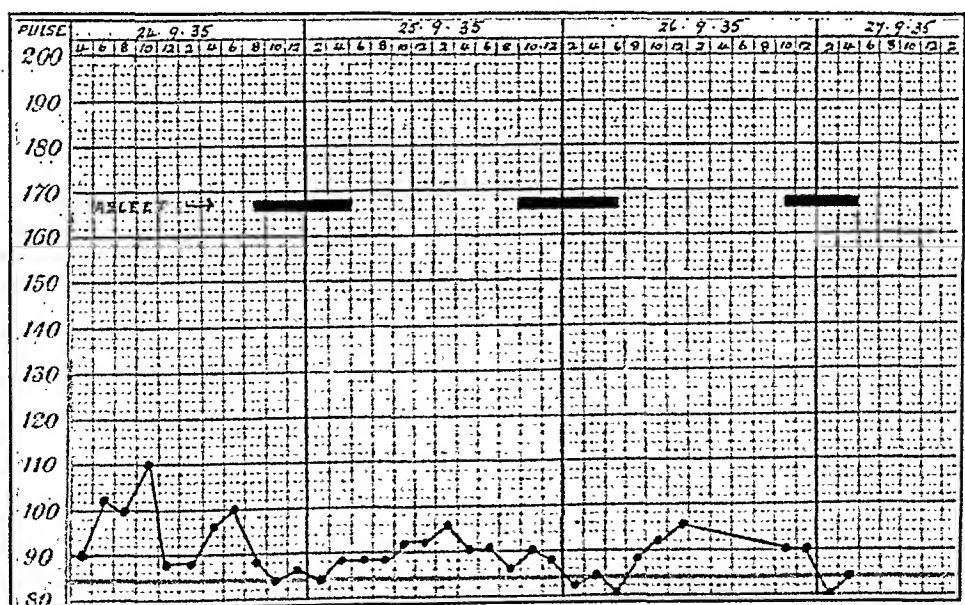
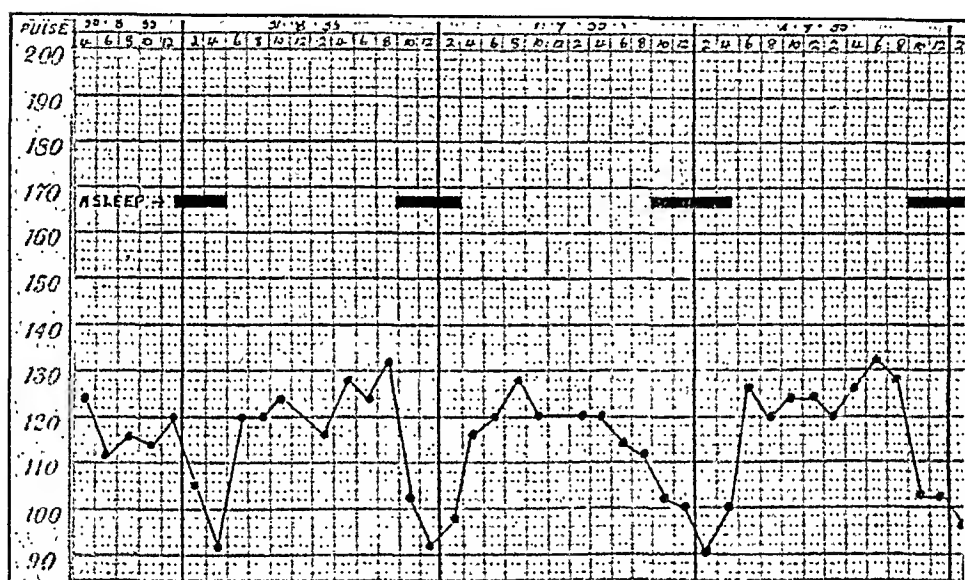
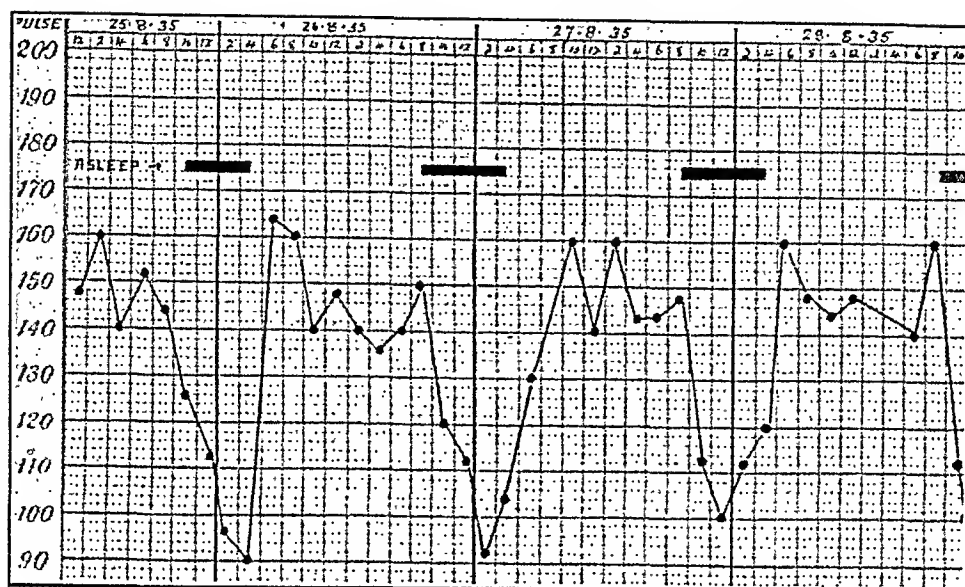


Fig. 7.—Showing progressive slowing of the pulse rate which approaches normal during the period of sleep, due to partial auriculoventricular block.



clinical and pathological associations, and the prognosis, of typical auricular and nodal tachycardia are so close, that from a practical viewpoint the distinction becomes confined to one of academic interest.

The locus of new impulse formation is of importance in relation to therapy directed toward abolition of the attack by stimulation of the vagus. After study of a patient exhibiting two irritable areas in the auricle, one near the auriculoventricular node, Carr<sup>3</sup> states that right carotid sinus stimulation will exert a greater effect upon nodal than upon sino-auricular rhythm. It is to be expected, however, that a tachycardia arising in or around the sino-auricular node would be more susceptible to right vagal influence. In Carr's patient, right carotid pressure caused ventricular standstill lasting 6.2 sec. In the present instance it was presumed that the new rhythm arose close to the normal pacemaker, as it was readily altered by stimulation of the right carotid sinus (Fig. 2), the P-R interval was equivalent to or even greater than normal, and the mode of termination, by lysis as it were, was of the nature usually represented by "nomotopic" tachycardia. The failure of vagal stimulation to diminish the heart rate and reestablish normal rhythm is perhaps due to the low grade of irritability of the cardiac muscle at the site of impulse formation and to continued depression after the actual vagal stimulation has ceased. Our chief difficulty is to reconcile the curious character of the new auricular complex with impulse formation at the sino-auricular node. One of the most constant criteria for a diagnosis of sino-auricular tachycardia is the preservation by the auricular complex of its normal configuration, and it has been held as axiomatic that an auricular complex of altered form denotes a site of impulse formation remote from the sino-auricular node, whether the arrhythmia is an extrasystole or a tachysystole. An isolated observation of Rothberger and Winterberg<sup>4</sup> is of interest in this regard. By stimulation of the peripheral sympathetic nerve supply to the heart on the left side, P-wave inversion appeared. In a heart rendered irritable by barium chloride, an attack of heterotopic paroxysmal tachycardia followed. It is a common experience, however, to observe, especially in the third lead, a negative or diphasic P-wave, in an otherwise completely normal tracing, and from an individual who is otherwise cardiologically sound. The particular alterations in the auricular complex in the patient under consideration, persisted long after the heart rate fell to under 100 per minute. Even weeks later, when the P-wave was again of the usual upright type, it was possible to detect a suggestion of its former deformity, especially in Lead III. Considered from this point of view, distortion of the auricular complex alone seems to be insufficient reason for excluding the presence of sino-auricular tachycardia. Boden<sup>5</sup> has described a patient in whom attacks of tachycardia occurred without any alteration whatever in the form of the P-wave or remainder of the curve—the pulse simply rising periodically

from 44 to 170 per minute. Galli<sup>6</sup> believes that attacks of "neurogenic" origin can arise in the normal pacemaker, and are more readily affected by vagal stimulation.

It is suggested that the patient under discussion in this paper suffers from a form of tachycardia in the genesis of which the extrinsic cardiac nerves take the major share. The reasons for this are that even during the height of the attack, emotion (such as on entering the hospital grounds), exercise, and sleep produced marked effects upon the rate and rhythm of the heart. Carotid sinus pressure failed to retard the auricular rate but produced a varying block.

A search of the literature reveals very little reference to attacks of paroxysmal tachycardia which are cardiographically heterotopic and yet which have a gradual, rather than an abrupt, ending. Marvin<sup>7</sup> has written an interesting account of a male arteriosclerotic patient whose first attack of ventricular tachycardia, with a rate of 174, subsided gradually over a period of eight days. The onset was sudden with oppression and palpitation. The subsequent occurrence of fever and leucocytosis and later of typical cardiographic changes of coronary occlusion of the  $T_1$  type leave no doubt that this was the precipitating factor in his patient. A second attack of tachycardia ended abruptly, but a third required quinidine. Our patient is therefore most uncommon in this particular.

#### SUMMARY

An attack of paroxysmal tachycardia in a female adult is described, which to our certain knowledge endured for sixty-nine days. The seizure was sudden in onset but gradual in decline. The cardiogram was typical of auricular paroxysmal tachycardia, but an unusual character of the auricular complex persisted for some time after the heart rate had returned to normal. This, together with the fact that the rhythm showed partial response to rest, exercise, emotion, and sleep, suggests that the case is of an intermediary character between nomotopic and heterotopic tachycardia.

I wish to express my thanks to my technician, Miss Scott, and to Dr. Crighton Bramwell and Professor C. G. Lambie for their encouragement.

#### REFERENCES

1. White, P. D.: Heart Disease, New York, 1931, The Macmillan Company, p. 641.
2. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1925, Shaw and Sons, p. 240 et seq.
3. Carr, F. B.: Auriculoventricular Nodal Paroxysmal Tachycardia and Auricular Flutter. Case Report, *AM. HEART J.* 7: 668, 1932.
4. Rothberger, C. J., and Winterberg, H.: Ueber die Beziehungen der Herznerven zur Form des E. K. G., *Arch. f. d. ges. Physiol.* 135: 506.
5. Boden, E.: Ueber den Einfluss der langen Herznerven auf die Form des Elektrokardiogramms in einer Fall von Paroxysmal Tachykardie, *Deutsches Arch. f. klin. Med.* 130: 249, 1919.
6. Galli, G.: Sur les Mecanismes de Terminaison et de Debut des Accés dans la Tachycardie Paroxystique (Nomotope), *Arch. d. mal. du coeur* 12: 289, 1919.
7. Marvin, H. M.: Unusual Example of Paroxysmal Tachycardia With Gradual Slowing of the Rate, *Heart* 10: 279, 1923.



## PUBERTY AND PROGNOSIS IN RHEUMATIC FEVER\*†

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THIS study is concerned with the relationship of age to susceptibility and resistance in rheumatic fever. It is based upon the study of a series of children who have been followed through childhood and adolescence; the age incidence of first and recurrent attacks of rheumatic fever has been recorded with a view to determine whether or not there is a period of life at which the recurrences become less frequent.

Primarily, rheumatic fever is not a disease of childhood per se if considered from the standpoint of the years of crippling morbidity which it may induce and the death rate. It is, however, a disease of childhood from the standpoint of the incidence of first attacks, for there is considerable evidence that, in urban populations at least, the majority of first attacks occur between the ages of five and twelve years.<sup>1-6</sup> Furthermore, although it is a disease which is subject to recurrences, there is also some evidence that if a primary attack has been sustained during childhood, recurrent attacks are more apt to arise during this period than later. Thus Swift<sup>7</sup> states that a condition of resistance seems to develop about the age of puberty. Willis<sup>8</sup> presents suggestive evidence that recurrent rheumatic infections are most frequent in the first decade of life and von Eickstedt<sup>9</sup> pointed out that reactivations occur less often after puberty. Stroud<sup>10</sup> has concluded that the primary manifestations and reactivations of rheumatic fever are more apt to occur between the ages of six and ten, and in a previous communication from this clinic<sup>11</sup> it was noted that after the age of seven years, recurrences decreased as age increased. The most extensive study of this subject is that of Wilson, Lingg, and Croxford<sup>4</sup> who, in a large series of cases, record fewer obvious recurrences after the ages of eleven or twelve years than before. The present study will deal with this decline in recurrent attacks which seems to occur at or shortly before puberty.

The clinical material available consisted of a group of 500 patients who had sustained one or more known attacks of rheumatic fever. All of them had been admitted to the New Haven Hospital or Dispensary at some time and most of them had been followed for several years in various cardiac clinics of the New Haven Dispensary.‡ The

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†The expenses of this investigation have been partially defrayed by the Milbank Memorial Fund.

‡We are indebted to the Department of Pediatrics of the Yale University School of Medicine and in particular to the members of the staff of the Pediatric Cardiac Clinic for assistance in this work and for the privilege of transcribing data from their records.

caliber of the material may differ from that described in previous similar studies in at least two respects: (1) the acquisition of rheumatic heart disease was not requisite for admission to the group, for many of the patients had had one or more attacks of rheumatic fever without detectable evidence of carditis; and (2) the patients were originally drawn from various clinics of a general hospital and not merely from a pediatric clinic—in other words, the age distribution of the group was not artificially weighted by a factor of selection on the basis of age.

Major criteria used for the diagnosis of active rheumatic fever in this group included the following manifestations: Sydenham's chorea, characteristic types of polyarthritis, subcutaneous nodules, and active rheumatic heart disease. Other signs and symptoms of supplementary value in determining the activity of the disease have included: erythema multiforme, frequent nosebleeds, otherwise unexplained fever and leucocytosis, and failure to gain weight.

It is well known that it is often difficult to determine accurately the age of onset of an attack of rheumatic fever. This is particularly true when the initial signs consist of growing pains or some of the supplementary diagnostic features mentioned above. We were, however, aided by one fact in making this determination, namely, that many of these patients had attended the New Haven Dispensary at intervals from the time of birth, and a more or less continuous record was available to supplement the story obtained at the time of an acute illness.

A recurrence has been defined as a period of activity of the disease occurring after eight to ten months or more of freedom from symptoms following a previous attack of rheumatic infection. For statistical purposes, only one attack per year has been included because of the difficulty of determining when one short attack has ended and another has begun if they occur within a period of a few weeks or months. In the rare instances when an attack lasted more than one year, the year of the onset only was included.

The ages of thirteen to fifteen inclusive have been chosen as the age period of puberty.

#### RESULTS

*The Age Incidence of First Attacks.*—The ages at which members of the group of 500 patients sustained their first attacks of rheumatic fever and the ages at which heart disease was first detected are shown in Fig. 1. Three hundred and fifty-eight [71 per cent] developed rheumatic heart disease. This gives a fair idea of the caliber of the clinical material under observation with respect to age and the general severity of individual cases. It will be seen that, in accordance with the findings of other investigators, the highest incidence of initial attacks of

rheumatic fever in this group lies between the ages of five and eleven years. It will also be seen that there is a sharp drop both in the incidence of first attacks of rheumatic fever and also in the development of heart disease during the two or three years immediately preceding puberty.

*Age Incidence of Second and Third Attacks.*—One hundred of the patients have been studied more carefully. The criteria for their selection were: that the initial attack occurred before the thirteenth year of age; that there had been at least one recurrence; that they had been followed in the out-patient department or hospital for at least five years subsequent to the first attack; that they had been followed through the fourteenth year of life. Over 50 of these patients were followed for ten years subsequent to their initial infection.

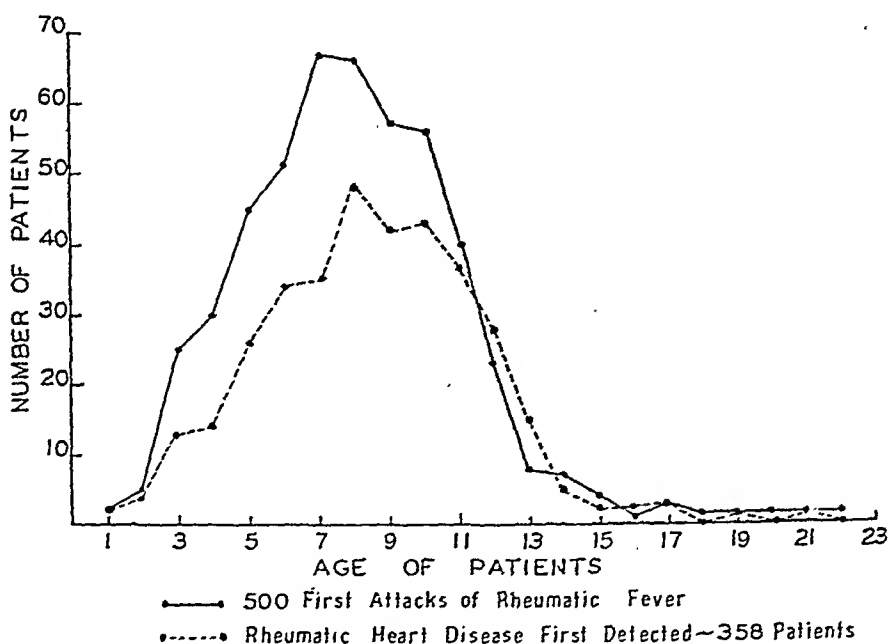


Fig. 1.

In Fig. 2 the relationship of first, second, and third attacks of rheumatic infection to the age of the patient is shown. As stated, all these patients had at least one recurrence; 60 of them had a second recurrence. It is to be noted that the period of greatest frequency of first recurrences falls between the ages of eight and thirteen years, and of second recurrences between nine and fourteen years. It is also apparent that a fairly sharp drop in frequency occurs for both second and third attacks between the thirteenth and fifteenth years.

From a study of these curves it is not clear whether or not this sharp decline in secondary and tertiary attacks, which occurs at about the age of fourteen years, is wholly dependent upon the age distribution of first attacks, for it is known that recurrences are more apt to follow shortly after a primary attack (i.e., within the first three to five

years<sup>6</sup>) than later. An alternative explanation is that regardless of the age of onset, this decline is an expression of gradually increasing resistance to the disease.

In an effort to secure further information relating to this question, the following analysis was made. Three groups of patients, who had

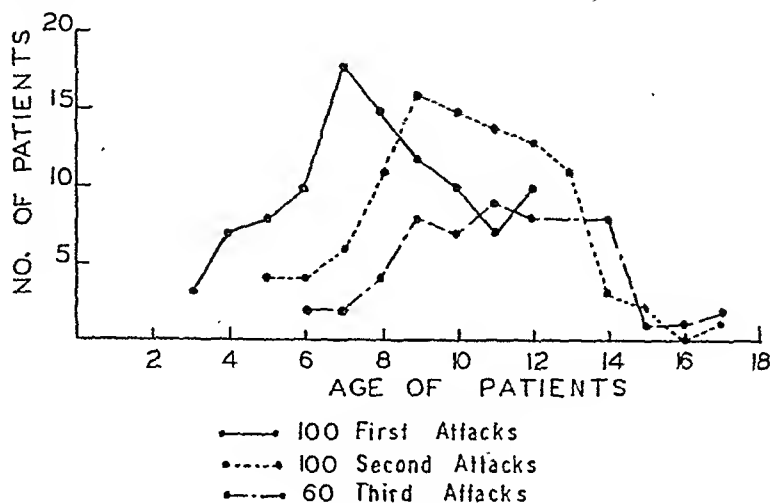


Fig. 2.

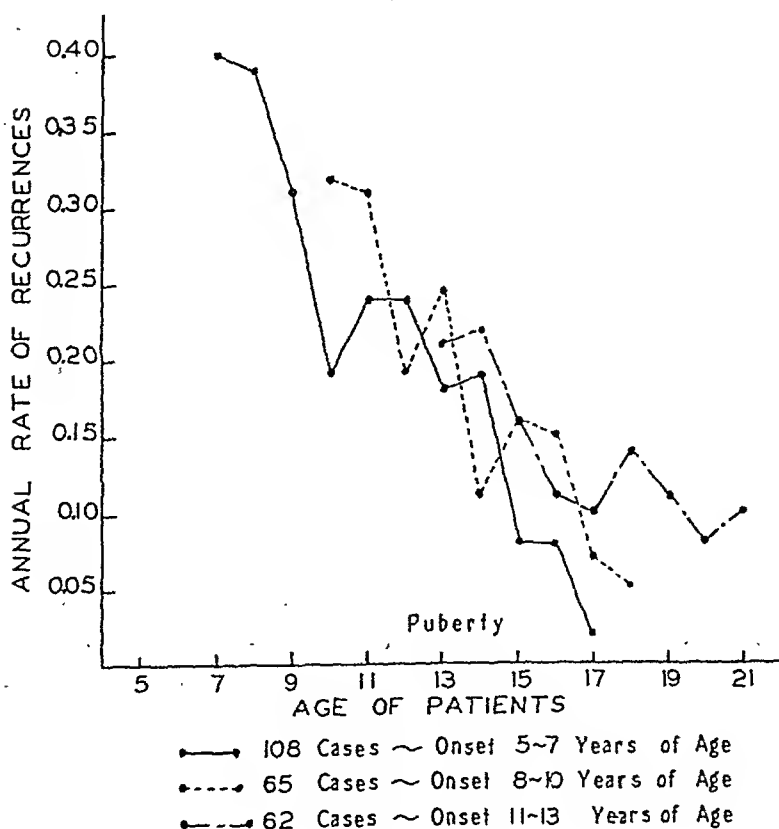


Fig. 3.

sustained their first attacks at different periods of childhood and who had been followed from five to thirteen years, were selected. The first attack occurred between the ages of five and seven years in 108 patients, between eight and ten years in 65 patients, and between eleven and thirteen years in 62 patients. In some cases a period of activity

during a given year has been estimated on the basis of history alone where physical examination was impossible; this has been recorded as one-half (0.5) a recurrence. The annual rate at which recurrences developed was determined in these three groups and is presented graphically in Fig. 3.

The curves here point to the fact that susceptibility (as judged by recurrent attacks) declines rather steadily as age increases over the period from seven to seventeen years. This decline, though definite, is quite gradual throughout this ten-year period. The configuration of the curves tends to minimize any sharp salutory effect upon the susceptibility to the disease which may come to pass during the age period of puberty, or one that is brought about by special physiological changes occurring at that time. They show, in other words, that the rates of recurrence are at least partly dependent upon the fact that a recurrence is more apt to follow close upon the heels of a primary attack than at some later time.

#### COMMENT

It has been recorded in this paper that just as first attacks of rheumatic fever show a sharp decline in frequency preceding the age of puberty, so also do recurrent (second or third) attacks show a decline during or just after the same age period. Factors responsible for this decline will probably remain unknown as long as the pathogenesis of rheumatic fever remains obscure, but one may note two influences which seem to contribute to it: that is, two influences which lend themselves to some degree of analysis. One of these is the fact that inasmuch as there is a sharp decline in primary attacks before the age period of puberty, there will be a sharp decline in recurrent attacks during the years immediately following, for recurrent attacks are more apt to follow close upon the heels of a primary attack.<sup>6</sup> However, this is not entirely responsible for the improvement noted at puberty in this disease, for another contributing factor is apparent in the analysis of groups of patients who had sustained their first attacks at different periods of childhood. A gradual decrease in susceptibility occurs, which covers the ten-year period following the ages of seven to nine years. These two factors then, and possibly others, chance to coincide at about the age of puberty to cause a distinct lessening of the number of recurrences.

The recognition of this improvement at the age of puberty is of some value in prognosis.

#### SUMMARY

The attempt has been made in this paper to analyze factors which bring about a sharp decline in recurrences of rheumatic fever at or about the age period of puberty.

Knowledge of the mechanism of this decline in susceptibility is limited, but two probable contributing factors have been noted and discussed.

Regardless of the mechanisms at work, the knowledge that improvement often occurs at puberty is of practical value in estimating the prognosis in rheumatic fever.

#### REFERENCES

1. Poynton, F. J.: Observations on the Nature and Symptoms of Cardiac Infection in Childhood, *Brit. M. J.* 1: 249, 1918.
2. Coombs, C. F.: Rheumatic Infection in Childhood, *Lancet* 1: 579, and 634, 1927.
3. Mackie, T. T.: The Prognosis and Treatment of the Rheumatic Infection, *AM. HEART J.* 3: 31, 1927.
4. Wilson, M. G., Lingg, C., and Croxford, G.: Statistical Studies Bearing on Problems in the Classification of Heart Disease. III. Heart Disease in Children, *AM. HEART J.* 4: 164, 1928.
5. Findlay, L.: The Rheumatic Infection in Childhood, New York, 1932, Wm. Wood & Company, p. 42.
6. Kaiser, A. D.: Factors That Influence Rheumatic Disease in Children, *J. A. M. A.* 103: 886, 1934.
7. Swift, H. F.: Factors Favoring the Onset and Continuation of Rheumatic Fever, *AM. HEART J.* 6: 625, 1930.
8. Willius, F. A.: A Study of the Course of Rheumatic Heart Disease, *AM. HEART J.* 3: 139, 1927.
9. Von Eickstedt, E.: Über den Einfluss der Pubertät auf die Residuihäufigkeit der Polyarthritidis acuta, *Zeitschrift für Kinderheilkunde* 56: 64, 1934.
10. Stroud, W. D., Goldsmith, M. A., Polk, D. S., and Thorp, F. Q.: Ten Years' Observation of Children With Rheumatic Heart Disease, *J. A. M. A.* 101: 502, 1933.
11. Paul, J. R.: Age Susceptibility to Familial Infection in Rheumatic Fever, *J. Clin. Investigation* 10: 53, 1931.

## EFFECTS OF EPINEPHRINE ON THE HEART\*

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EPINEPHRINE, in its action upon the heart, has a reputedly anomalous effect. Direct observations by Dueret,<sup>1</sup> on surviving vessel strips, disclosed that dilatation resulted from the application of a 1:100,000 solution of epinephrine. This author observed no reversal of the effect and he observed that a load on the vessel strip accentuated the epinephrine effect. Increased alkalinity diminished the response and increased acidity caused spontaneous dilatation. A temperature drop of one degree resulted in a decrease in the dilating effect of the epinephrine. This work is confirmatory of previous work on isolated coronary vessel strips.

Gollwitzer, Meier, and Krueger<sup>2</sup> on the basis of coronary flow experiments concluded that the sympathetics carry dilator fibers to the coronaries and that coronary dilatation follows the administration of epinephrine.

Klisiecki and Flek<sup>3</sup> studied the coronary flow with a photohemotachometer. Epinephrine, they concluded, acts as a vasoconstrictor on the coronary bed but this effect is nullified by the increased aortic pressure.

Anrep, Barsoum, and Talaat,<sup>4</sup> using the direct flow method on the coronary vessels, uniformly obtained an increase in the blood flow following the injection of epinephrine.

Melville<sup>5</sup> makes the following summarizing statement: "... coronary dilatation which undoubtedly follows the administration of many of these substances (ephedrine, adrenaline, histamine, and the nitrites)." This author presented further evidence of this effect by demonstrating that epinephrine and ephedrine are capable of abolishing the coronary constriction induced by posterior pituitary extract.<sup>6</sup>

The only direct observation on the heart following the administration of epinephrine was reported by Hurvitz and Smith.<sup>7</sup> These authors, in the course of experiments designed to study the effect of vasodilators following ligation of the coronary artery, found that the cyanosis which characterized the infarcted area was eradicated by the administration of theophylline. The cyanosis returned at once following the injection of 2 c.c. of 1:1,000 solution of epinephrine.

Electrocardiographic changes induced by epinephrine were described by Kahn<sup>8</sup> as directional changes in the T-wave. Later authors<sup>9</sup> de-

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scribed inversion of the QRS, "W" form of the QRS and elevation of the S-T interval following the injection of 1 c.c. of a 1:100,000 solution of epinephrine. Bartos and Burstein<sup>10</sup> observed inversion of the T-wave following the administration of 1 to 2 c.c. of a 1:100,000 solution of epinephrine, as well as following stimulation of the cerebral end of the cut vagus. Katz<sup>11</sup> induced precordial distress in two of six normal subjects following the administration of epinephrine. He precipitated moderate but typical pain and distress in two patients and a severe attack in a third case of known angina pectoris by the administration of this drug, substernal and precordial pain in a case of luetic aortitis and distress in an "irritable heart" subject. The electrocardiographic changes observed following the administration of epinephrine were chiefly downward deviation of the S-T interval and diminished amplitude of the T-wave.

Petzetakis<sup>12</sup> studied the effects of various sized doses of epinephrine in rabbits from the standpoint of the electrocardiographic changes induced. He noted slowing of rate following the administration of small doses of epinephrine intravenously. Larger doses induced extrasystoles, in addition to the bradycardia. As the dose was further increased this latter effect became more pronounced until lethal doses of epinephrine caused flutter or fibrillation of both the auricles and ventricles and bundle-branch block of varying degrees.

Stella<sup>13</sup> proved that the bradycardia induced by epinephrine is due to the effect of the blood pressure rise on the carotid sinus mechanism.

Anrep, Barsoum, and Talaat<sup>4</sup> demonstrated a marked increase in the histamine production by the myocardium, following the administration of epinephrine, independent of blood pressure, rate, or rhythm effects.

Frischi<sup>14</sup> demonstrated an increase in the water content of the myocardium after the administration of epinephrine.

Levy,<sup>15</sup> and Whitehead and Elliott,<sup>16</sup> demonstrated the increased capacity of epinephrine to induce ventricular fibrillation in animals under chloroform anesthesia.

Rosenblum, Hahn, and Levine<sup>17</sup> demonstrated an increased sensitivity of the heart to epinephrine after feeding thyroid extract.

Wiggers<sup>18</sup> states that epinephrine causes acceleration of conduction in the ventricles. The same author<sup>19</sup> states categorically that epinephrine causes constriction of the coronaries.

Angina pectoris, whether of spastic or sclerotic origin, is characterized from the electrocardiographic standpoint by either directional changes in the T-wave or deviation of the S-T interval from the isoelectric line, or both. These electrocardiographic changes are due to changes in the myocardium resulting in disturbances in the pathways of retreat.<sup>20</sup>

Similar changes have been brought about by anoxemia; Greene and Gilbert<sup>21</sup> caused shortening of the P-R and R-T intervals and decreased



amplitude or directional changes in the T-wave in normal humans by marked anoxemia. Kountz and Gruber,<sup>22</sup> and Kountz and Hammouda,<sup>23</sup> obtained similar results in experimental animals. Tigge<sup>24</sup> described as the characteristic changes induced in the human by reduced oxygen content of the inspired air an increased pulse rate, shortening of the P-R and R-T intervals, increased height of the P-wave, and flattening to inversion of the T-wave. These changes disappeared at once when adequate oxygen was supplied. Katz, Hamburger, and Schatz<sup>25</sup> carried out similar experiments with the same results. They were also able to induce more pronounced changes in four out of six cases of angina. The latter observation has also been made by Dietrich and Schweigk.<sup>26</sup> Pain was not a necessary accompaniment of the electrocardiographic changes so induced. Creip<sup>27</sup> observed directional changes in the T-wave and changes in level of the S-T interval during anaphylactic shock and postulated myocardial anoxemia as the cause. Anginal pain with inversion of the T-wave and displacement of the S-T interval was noted in the absence of pathological changes in the coronary vessels in a case of severe anemia by Elliot.<sup>28</sup>

#### EXPERIMENTS

A series of experiments was designed to determine the mechanism of the epinephrine effects on the heart as indicated by the changes induced in the electrocardiogram.

The general procedure included the comparative effect of injection of epinephrine into a systemic vein and a coronary artery as well as the effect of epinephrine before and after vagotomy.

Dogs were anesthetized with nembutal administered intraperitoneally. The coronary artery was exposed in the following manner for the intracoronary injection:

A curved incision with the convexity toward the midline was made extending from a point about 1 cm. caudad to the apex beat to the level of the fourth rib. The pectoral muscles were divided between clamps, two or three ribs were severed, and the pleural cavity opened. A respiratory pump connected with the trachea was started at this point.

The pericardial sac was opened and tension on its edges served to lift the heart into the field. The epicardium overlying the anterior descending branch of the coronary artery was grasped with mosquito forceps and divided, exposing the vessel. Injections were made through a 26 gauge needle. The bleeding which occurred after the withdrawal of the needle was controlled by pressure applied for a few moments over the bleeding point.

Electrocardiograms were made using Lead II, before, during, and at intervals after the injections. Control tracings were made after inserting the needle and after injecting normal saline. In some of the experiments simultaneous carotid pulse tracings were made by means of a Hürthle manometer whose arm threw its shadow on the camera slit of the electrocardiograph. The following dilutions of epinephrine were used: 1:250,000; 1:50,000; 1:25,000; 1:10,000 and 1:1,000. Rather wide variations in the degree of response were encountered in the individual animals. Qualitatively, however, the changes were uniform. An electrocardiogram from each group displaying the characteristic, marked changes will be described in detail.

Experiment IX. 1:250,000 solution of epinephrine (Fig. 1.).

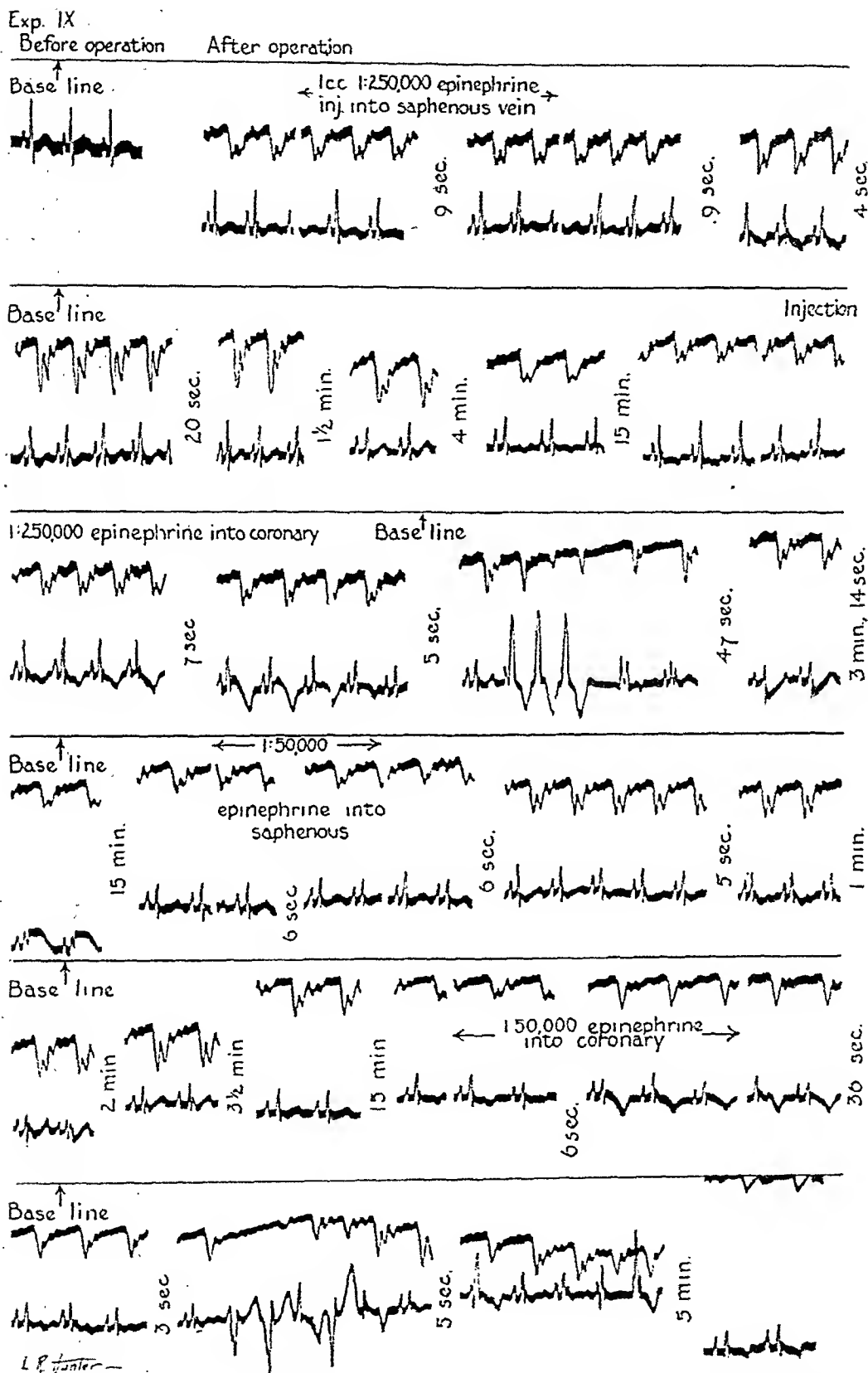


Fig. 1.—One cubic centimeter of 1:250,000 and 1:50,000 solution of epinephrine each injected into the saphenous vein and the coronary artery. Note that pulse tracing is inverted.

In the control tracing the PQR was normal, the S was rather deep, and the T, upright. A second tracing was made immediately after the chest was opened and the carotid incannulated. The T-wave had become isoelectric. There were no variations in the pulse record.

One cubic centimeter of 1:250,000 solution of epinephrine was injected into the saphenous vein during a period of seventeen seconds. The blood pressure began to rise twenty seconds after the completion of the injection. Three seconds later the T-wave became diphasic for several beats and then definitely inverted. The S-T interval became depressed, arising from an elevated take-off; the T again became diphasic but the S-T interval remained depressed during the succeeding one-half minute. The pulse curve heralded these changes by a gradual increase in diastolic and systolic pressures. After fifteen seconds, the diastolic pressure had returned to its original level and during the succeeding beats dropped below it. The systolic pressure, however, continued at the maximum level or only slightly below. The primary oscillations of the injection phase became more prominent and more sharply separated. The rate increased from 120 to 140 during this period. The electrocardiographic tracing continued to display a high T-wave with a depressed S-T during the succeeding two minutes; it then became diphasic and finally inverted. The pulse wave gradually returned to its original level and configuration.

Ten minutes after the first injection 1 c.c. of 1:250,000 epinephrine solution was injected into the coronary artery over a period of sixteen seconds. Within a few beats after the injection was begun the blood pressure began to rise and simultaneously the milliamperage of the already inverted T-wave began to increase and its take-off became elevated, both features becoming very pronounced before the injection was completed. After the completion of the injection the T-wave became diphasic for a few beats and then upright from a depressed take-off.

The pulse curve showed little change other than a moderate elevation in pressure. This returned to the original level fourteen seconds after the completion of the injection. At this point a series of three ventricular extrasystoles was recorded, followed by a notched R-wave and an inverted T. The T-wave then became upright. The pulse tracing displayed single small ejection waves corresponding to the ventricular extrasystoles and a drop in the pressure level during this period.

Seconds later the take-off of the T-wave became markedly depressed. Five minutes after the injection was completed the S-T interval rose to a point above the isoelectric line. This lasted for another minute when the T-wave again became depressed.

A second injection of 1 c.c. of 1:250,000 epinephrine was made into the coronary artery over a period of fourteen seconds. An elevated take-off to a deeply inverted T-wave developed during the injection, gradually becoming less and less prominent during the subsequent four seconds, then three ventricular extrasystoles occurred followed by a series of waves characterized by an elevated S-T convex to an inverted T. A single ventricular wave was interpolated into this group. Gradually the S-T segment dropped, the T remained inverted. The blood pressure rose during the injection. After its completion the pulse waves became less prominent and, corresponding to the first ventricular extrasystoles, the blood pressure dropped sharply, remaining at a low level for fourteen seconds when it again rose to a point slightly above its previous level.

During the subsequent five minutes the S-T interval remained elevated, rising convexly to an inverted T-wave.

After another few minutes the S-T returned to the isoelectric line and the T became upright.

One cubic centimeter of 1:50,000 epinephrine was injected into the saphenous vein over a period of fourteen seconds. Twenty-three seconds after the completion of the injection the blood pressure began to rise and the amplitude of the T-wave

increased slightly for a few beats. The T-wave then became diphasic for twelve seconds, then upright and its amplitude increased. The S-T interval was depressed and concave to an upright T. This gradually disappeared in the next four minutes leaving an upright T of low amplitude.

One cubic centimeter of 1:50,000 epinephrine was injected into the coronary artery over a period of twenty-one seconds. Prior to the injection, T was inverted and of small amplitude. Its amplitude began to increase, the take-off began to rise and the S-T interval became convex during the period in which the injection was being made. Simultaneously with the first change in the T-wave the blood pressure rose slightly but returned to its original level before the injection had been completed. The pulse curve began to change simultaneously with the rise in pressure and soon was characterized by a single clean-cut upthrust of the ejection phase followed by a series of small oscillations. Six seconds after the completion of the injection the pressure again began to rise and corresponding to this the amplitude of the T-wave became less. Forty seconds later the T-wave became diphasic, followed by a series of ventricular extrasystoles associated with a drop in blood pressure. With their passage the blood pressure again rose. These changes were followed by an irregular series of beats with upright, inverted and diphasic T-waves and ventricular extrasystoles. This persisted for a minute when the tracings again became regular with a small inverted T-wave. The blood pressure, after four minutes, began to fall, reaching a level much lower than the original.

One cubic centimeter of 1:10,000 epinephrine was injected into the saphenous vein over a period of 18 seconds. Twenty seconds after the completion of the injection the blood pressure began to rise and the previously low amplitude T-wave increased, and the S-T interval became depressed and concave. T soon became diphasic. Forty-five seconds after the completion of the injection a series of ventricular extrasystoles occurred followed by ventricular fibrillation.

Experiment V. Control: Rate, 178; P, 0.3 mv.; T, upright; 0.2 mv.

One cubic centimeter of 1:25,000 epinephrine was injected into the saphenous vein over a period of twenty-three seconds. Five seconds after the injection had begun T and P began to approach each other so the T-P interval became "V" shaped with the apex above the isoelectric line. This became more pronounced so that nine seconds after the injection was begun T and P formed an "M" shaped curve. The voltage of the T-wave gradually diminished and it became diphasic with its initial deflection downward. The rate had increased to 210. This curve persisted for about a minute. Two and one-half minutes after the injection had been completed the T had become upright again and two minutes later the curve had returned to its original configuration.

One cubic centimeter of 1:10,000 epinephrine was now injected into the saphenous vein during a period of six seconds. The resulting changes in the curve were similar to those described above but quantitatively more marked. These changes persisted several minutes longer than after the first injection.

Experiment VI. Control: Rate, 170 (Fig. 2).

Configuration normal. Isolation of the coronary artery and insertion of the needle caused a slight increase in voltage of T and P and the rate increased to 176.

One cubic centimeter of 1:25,000 epinephrine solution was injected into the anterior descending branch of the left coronary artery over a period of fifteen seconds. Nine seconds after the injection was begun notching of the R-wave developed and the voltage of the T-wave began to increase. The T-wave became irregular in that its outline varied and the level of the S-T interval varied. This type of curve persisted for thirty seconds and then gradually returned to normal one minute after the completion of the injection. During another minute occasional "W" shaped R-waves occurred. The maximum rate was 175.

Control: Upright, T; normal configuration; Rate, 93.

One cubic centimeter of 1:10,000 solution of epinephrine was injected into the saphenous vein over a period of 19 seconds during which time the blood pressure and cardiographic curves remained unchanged. Eight and two-tenths seconds after completing the injection three ventricular extrasystoles occurred during which the pulse pressure was diminished. Twenty-three seconds after the completion of the injection the T-wave became diphasic and two beats later definitely became inverted and the S-T interval depressed. Corresponding to the first changes in the T-wave the systolic, diastolic, and pulse pressures rose. This phase lasted five seconds.

Exp. VI

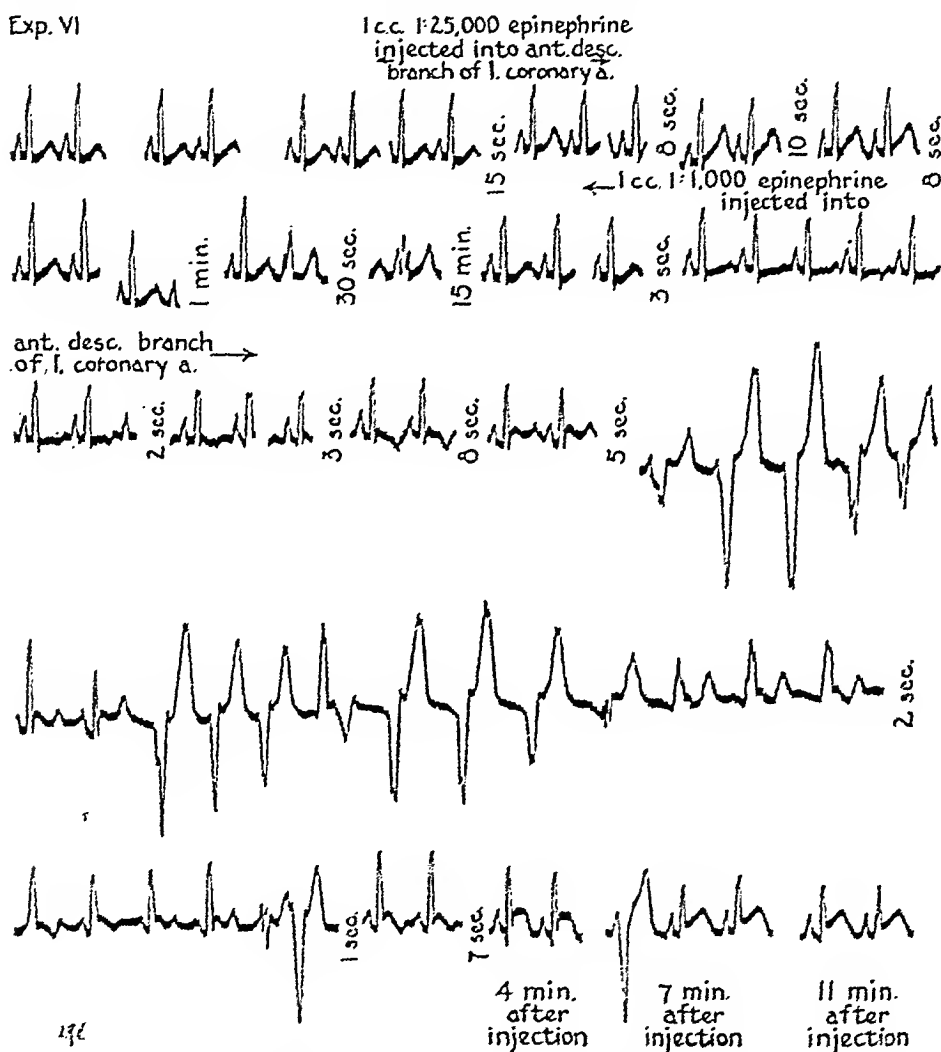


Fig. 2.—One cubic centimeter of 1:25,000 epinephrine solution injected into the saphenous vein and the coronary artery.

During the succeeding seven seconds the systolic and diastolic pressures continued to rise but the pulse pressure diminished. The electrocardiogram continued to display an inverted T and depression of the S-T interval. There then occurred a series of ventricular contractions characterized by a prominent QRS and a deeply inverted T-wave lasting six and one-half seconds during which time only one auricular contraction was recorded. Except for a beat corresponding to the auricular contraction the carotid pulse curve failed to show a pulse wave, and, except for a small rise soon after the onset of the ventricular complex, the blood pressure dropped.

The rate now became somewhat slower, and, corresponding to the return of the P-wave, pulse waves were again recorded. The T-waves remained inverted and of varying but usually high voltage. P-waves came through at irregular intervals. The systolic, diastolic, and pulse pressures increased and the rate dropped to 55. A pause, lasting two seconds, was followed by a complete cycle with a diphasic P-wave. The pulse curve was variable but was maintained with an increased systolic, diastolic and pulse pressure.

After an interval of several minutes the pulse curve had returned to the original level.

One-half cubic centimeter of 1:10,000 solution of epinephrine was injected into the coronary artery. Three seconds after the completion of the injection a ventricular extrasystole occurred associated with a drop in blood pressure. This wave did not come through on the pulse curve. The succeeding beats could not be interpreted in the cardiograph because of the extrinsic interference until twenty-five and one-half seconds after the injection had been completed when the T-wave became diphasic, then inverted for a few beats, and again diphasic. This curve persisted for several minutes. The pulse curve remained unchanged throughout.

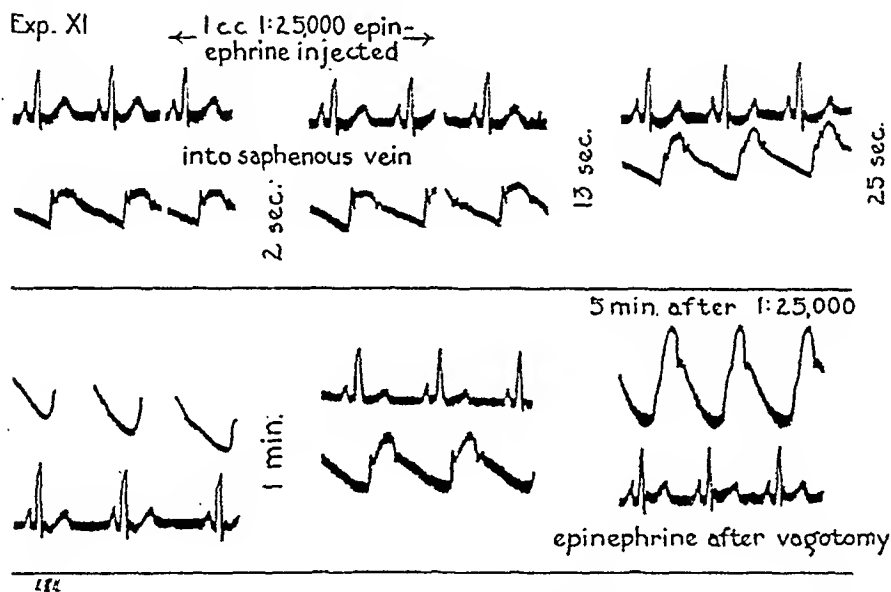


Fig. 3.—One cubic centimeter of 1:25,000 solution of epinephrine injected into the saphenous vein before and after vagotomy.

Experiment VIII. Control: Rate, 170; T, upright; configuration normal.

One cubic centimeter of 1:1,000 epinephrine solution was injected into the saphenous vein during a period of six seconds. At the completion of the injection the rate increased to 200 for several beats and the T-wave became isoelectric. The rate then slowed and the T became upright and of increasing voltage. The P-R interval varied from 0.08 second to 0.40 second and R became notched. The rate then stabilized at 75. At this time the T-wave was of high voltage and the P-wave was absent. This continued for one minute. The rate then rose rapidly, the QRS became inverted and the upright T increased in voltage to over 1 mv. and no P-waves were recorded. The rate stabilized for a minute at 235 to 260. Four minutes after the completion of the injection the rate was 270, the QRS was inverted, the S-T interval elevated, T upright and of moderate voltage, and no P-wave was apparent. A minute later R was again upright, S-T elevated, and T of low voltage. During the succeeding three minutes T again increased and R diminished in voltage. At the end of this period a series of bizarre ventricular waves was recorded, followed by another series of ventricular complexes lasting about forty-five seconds and charac-

terized by inversion of QRS and a high voltage upright T-wave. These gave way to a series having an upright R of rather low voltage and an upright T. Gradually the rate slowed to 157, and the P-wave reappeared. R was still of low voltage and S-T was elevated. Ten minutes after the injection the rate was 140, P present, R of low voltage, and S-T slightly elevated.

Experiment XI. Control: Rate, 103; P, 0.4 mv.; Q, obscure; R-Q mv.; S, deep; S-T, depressed 0.05 mv.; T, 4.5 mv. (Fig. 3).

One cubic centimeter of 1:50,000 solution of epinephrine was injected into the saphenous vein over a period of seventeen seconds. During the last seconds of injection the blood pressure began to rise but shifting of the string prevented any accurate judgment of the electrocardiogram. Five seconds after the injection S-T was isoelectric and T was 5 mv. The rate was 93. The T-wave was still at 5 mv. at the end of fifteen minutes and the S-T interval had returned to a level slightly below the isoelectric line when 1 c.c. of 1:25,000 epinephrine was injected into the saphenous vein over a period of sixteen seconds. Six seconds after the completion of the injection the blood pressure began to rise. Ten seconds later the S-T interval became definitely depressed. Save for a few long beats the rate remained unchanged. The T-wave decreased to 0.3 mv.

Four minutes later the curve had entirely recovered its original configuration.

The vagi were cut and 1 c.c. of 1:25,000 epinephrine was injected into the saphenous vein. Due to technical difficulties only a short electrocardiogram was obtained several seconds later. This showed the S-T interval to be elevated and concave to an upright T. The S-T was isoelectric for several minutes but the T was the shape of a broadened and flattened "M."

One cubic centimeter of 1:25,000 epinephrine was injected into the saphenous vein over a period of twelve seconds. The blood pressure began to rise thirteen seconds after the completion of the injection and during the succeeding ten seconds the voltage of the T-wave diminished and twenty-five seconds after the injection the previously broad, flat "M" form of the T-wave disappeared leaving the usual type of wave. The S-T interval became depressed during this period. Ten seconds later the T-wave became diphasic, then inverted, then diphasic again, and finally upright, during a period of thirteen seconds. During the succeeding forty-six seconds the voltage of the T-wave diminished and the blood pressure reached its maximum as did the pulse pressure. At the end of this period the T-wave was isoelectric. This persisted for a few beats when a very small inverted T-wave could be discerned becoming more prominent, and gradually becoming upright with an elevated S-T interval. Fifteen minutes after the injection the T-wave had resumed its broad, flat "M" form.

Experiment X. Control: Rate, 203; P, 0.5 mv. 0.04 second; P-Q, 0.04 second; Q, inconspicuous; R, 0.7 mv. 0.02 second; S, prominent 0.3 mv.; S-T, isoelectric 0.04 second; T, upright 0.5 mv. 0.06 second (Fig. 4).

Pulse wave—pressure constant. One cubic centimeter of 1:50,000 solution epinephrine was injected into the saphenous vein over a period of thirteen seconds. No change followed this injection.

One cubic centimeter of 1:25,000 solution epinephrine was injected into the saphenous vein over a period of thirty seconds. The diastolic pressure rose slightly at the completion of the injection as did the systolic. The T-wave became diphasic three seconds after completion of the injection and inverted 6 beats later. The blood pressure began to rise three seconds after the T-wave became diphasic. The T-wave remained inverted for twenty-two seconds when it became diphasic for four and one-half seconds. During this period the blood pressure had reached and maintained a very high level. The T-wave turned upright with a sharp apex. Its voltage gradually increased corresponding to a slight drop in the blood pressure,

reaching a maximum of 0.7 mv. in contrast to the preinjection level of 0.4 mv. The increased voltage of the T-wave persisted during the succeeding five minutes. The pulse rate decreased from a preinjection rate of 225 to 214, six seconds after the injection had been completed. During the succeeding ten minutes the T-wave remained somewhat elevated and the T-P interval took on an "M" form.

A second injection of 1 c.c. of 1:25,000 epinephrine into the saphenous vein over a period of fifteen seconds resulted in a transient diphasic T coming on five seconds after the completion of the injection corresponding to the beginning of the blood pressure rise. The diphasic T was replaced after two seconds by a depressed S-T interval. Simultaneously the voltage of the T-wave began to increase reaching a maximum of 0.7 mv. During the succeeding ten minutes the preinjection configuration of the blood pressure curve returned.

The vagi were cut without altering the configuration. The rate rose from 220 to 235. One cubic centimeter of 1:25,000 epinephrine was injected into the saphenous vein over a period of seventeen seconds. The blood pressure began to rise shortly before the end of the injection. Three seconds after the injection was completed

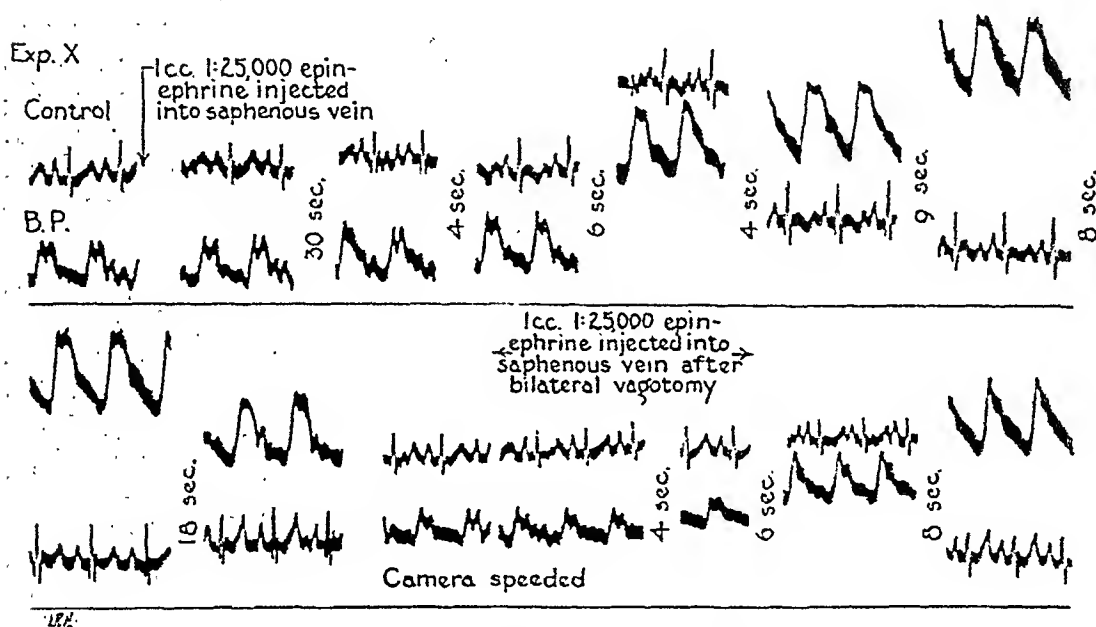


Fig. 4.—One cubic centimeter of 1:25,000 solution of epinephrine injected into the saphenous vein before and after vagotomy.

the T-wave became diphasic, remaining so for nine seconds when the S-T interval became depressed and the height of the T-wave began to increase. T-P took on an "M" form at this time. The configuration was gradually modified during the succeeding ten seconds until the T-wave reached a maximum of 0.7 mv., the S-T interval remained depressed and the T-P interval returned to the isoelectric line. The rate rose to 253.

Experiment XII. Control: Rate, 140; P, 4.5 mv.; Q, inconspicuous; R, 1.5 mv.; T, inverted.

One cubic centimeter of 1:50,000 epinephrine was injected into the saphenous vein. Eleven seconds after the beginning of the injection the form of the pulse wave developed a sharp, short ejection phase, and a drop in the pulse pressure and the systolic and diastolic blood pressures occurred. Corresponding to this the T- and P-waves became isoelectric, the latter reappearing after a few beats. The T-wave reappeared diphasic and then became upright corresponding to a rising diastolic, systolic, and pulse pressure. With the reappearance of the P-wave the pulse curve changed and the ejection phase became broader. After another fifteen



seconds the T-wave again became diphasic and then over another fifteen-second period inverted with an increasing voltage. Nine minutes after the injection the curve had returned to the configuration seen in the control.

Cutting the vagi resulted in a momentary pause but no subsequent change in the curves.

Strong vagal stimulation for 5.5 seconds stopped the heart momentarily. This was followed by a few slow beats with a marked increase in the voltage of the inverted T-wave. Mild vagal stimulation caused a marked decrease in the pulse waves and blood pressure but no change in the electrocardiogram.

One cubic centimeter of 1:50,000 epinephrine solution was injected into the saphenous vein over a period of nine seconds. The blood pressure rose slightly twenty-four seconds after the completion of the injection and, corresponding to this change, the S-T interval rose slightly and the voltage of the normally inverted T-wave diminished. Ten seconds after its initial rise the blood pressure dropped and the T-wave became diphasic for 8 beats, then upright for a few beats, again diphasic, inverted, diphasic, upright, isoelectric, and finally inverted.

After fifteen minutes 1 c.c. of 1:1,000 epinephrine solution was injected into the saphenous vein over a period of eight seconds. The T-wave became isoelectric five seconds after the completion of the injection corresponding to the beginning of the rise in blood pressure. At the same time the P-wave became markedly reduced in amplitude. The T-wave soon became inverted but the rate having increased to 200 the T and P were run together. The S-T interval rose and became convex to an inverted T and finally ventricular fibrillation set in.

#### DISCUSSION

The intravenous injection of a solution of epinephrine causes changes in the electrocardiographic tracing closely simulating those encountered in angina pectoris in which condition the myocardium but not the conduction mechanism is involved. There is a wide variation in individual susceptibility to the drug both in human subjects and in experimental animals. The minimal effect is a reduction in the amplitude of the T-wave. This is closely followed by the appearance of the diphasic form. Next, directional changes in the T-wave, i.e., a previously upright T becomes inverted or vice versa, or a marked increase in the voltage of the T-wave appears. Deviation of the S-T interval from the isoelectric line is often associated with these pronounced changes in the T-wave. Finally ventricular extrasystoles and, with very large doses of epinephrine, ventricular fibrillation set in. With very large doses of epinephrine transient conduction interference may occur.

These changes were induced with much greater regularity and as would be expected, by much smaller doses when the drug was injected into the coronary artery than when the injection was made into the saphenous vein. When given by the coronary route even small doses of epinephrine caused transient notching of the R-wave in some instances.

In every tracing in which both were recorded the blood pressure rise occurred simultaneously with or immediately preceded the most minute changes in the electrocardiographic tracing.

Division of the vagi served to increase the epinephrine effect.

Coronary flow experiments indicate that epinephrine causes an increase in the volume of blood passing through the coronary vessels. It is hardly an acceptable hypothesis that this increased blood flow through the coronaries would cause the electrocardiographic changes recorded after the injection of epinephrine.

Though generalized oxygen lack causes changes in the ventricular complex its most characteristic effect is first to speed up A-V conduction and later to slow it, in contrast to the primary effect of epinephrine on the ventricular musculature and its minor effect on conduction. Thus if the epinephrine effects observed were dependent entirely, or even largely, upon diffuse coronary constriction they should simulate oxygen deprivation effects more closely.

The changes encountered can only be accounted for by the following train of events.

Epinephrine, by increasing the demand of the myocardium for blood far beyond the increased availability resulting from increased coronary blood flow, causes a relative or functional anemia of the myocardium. This results in changes in myocardial action comparable to those of a normally functioning myocardium which is having its blood supply diminished. Because the changes encountered develop so rapidly they must be the result of relative myocardial anoxemia.

The contrast between the effects of generalized anoxemia and those of epinephrine is then to be explained by the fact that during the epinephrine effects the conducting mechanism received adequate blood since its demand for blood was affected but little.

These conclusions are supported by the accentuation of the epinephrine effect following section of the vagi. The removal of this inhibiting mechanism leads to further increase in myocardial activity and therefore greater oxygen need.

#### SUMMARY

Electrocardiographic studies were made after the injection of epinephrine into the saphenous vein and the coronary artery and following vagotomy. The electrocardiographic changes caused by epinephrine are ascribed to its increasing the myocardial requirements for oxygen beyond the available supply, thus resulting in functional anoxemia of the myocardium.

#### REFERENCES

1. Ducret: *Arch. f. d. ges. Physiol.* 225: 680, 1930.
2. Gollwitzer, Meier, and Krueger: *Pflüger's Arch. f. d. ges. Physiol.* 236: 594, 1936.
3. Klisiecki and Flek: *Ztschr. f. Biol.* 97: 7, 1936.
4. Anrep, Barsoum, and Talaat: *J. Physiol.* 86: 431, 1936.
5. Melville: *Arch. internat. de pharmacodyn. et de thérap.* 44: 316, 1933.

6. Melville, K. I.: *J. Pharmacol. & Exper. Therap.* 47: 355, 1933.  
Melville, K. I., and Stehle, R. L.: *J. Pharmacol. & Exper. Therap.* 42: 455, 1931.
7. Fowler, W. M., Hurvitz, H. M., and Smith, F. M.: *Arch. Int. Med.* 56: 1242, 1935.
8. Kahn: *Arch. f. d. ges. Physiol.* 129: 379, 1909.
9. Rosenblum, Hahn, and Levine: *Arch. Int. Med.* 51: 279, 1933.
10. Bartos and Burstein: *J. Lab. & Clin. Med.* 9: 217, 1924.
11. Katz, L. N.: *AM. HEART J.* 7: 371, 1931.
12. Petzetakis: *J. de physiol. et de path. gén.* 29: 428, 1931.
13. Stella: *J. Physiol.* 77: 68, 1932.
14. Frischi, A.: *Ztschr. f. d. ges. exper. Med.* 86: 408, 1923.
15. Levy, K. G.: *Heart* 4: 319, 1912-1913.
16. Whitehead, R. W., and Elliott, D. C.: *J. Pharmacol. & Exper. Therap.* 31: 145, 1927.
17. Rosenblum, Hahn, and Levine: *J. Pharmacol. & Exper. Therap.* 31: 145, 1927.
18. Wiggers: *J. Pharmacol. & Exper. Therap.* 30: 233, 1937.
19. Wiggers: *Physiology in Health and Disease*, Philadelphia, 1935, Lea & Febiger, p. 1036.
20. Katz, L. N.: *Physiol. Rev.* 8: 447, 1928.
21. Greene and Gilbert: *Arch. Int. Med.* 27: 517, 1921.
22. Kountz and Gruber: *Proc. Soc. Exper. Biol. & Med.* 27: 170, 1929.
23. Kountz and Hammouda: *AM. HEART J.* 8: 259, 1932.
24. Tigges: *Ztschr. f. Kreislaufforsch.* 28: 225, 1936.
25. Katz, L. N., Hamburger, W., and Schatz: *AM. HEART J.* 9: 771, 1934.
26. Dietrich and Schweigk: *Klin. Wchnschr.* 12: 135, 1933.
27. Crip: *Arch. Int. Med.* 48: 1098, 1931.
28. Elliot: *Am. J. M. Sc.* 187: 185, 1934.

# PRODUCTION BY EPINEPHRINE OF S-T CHANGES IN THE ELECTROCARDIOGRAM OF THE CAT, SIMILAR TO THOSE OF CORONARY OCCLUSION\*

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SIR THOMAS LEWIS, in collaboration with B. Gelfand, showed in 1935 that the thrombosis produced by ergot in the cock's comb was secondary to arterial spasm.<sup>1</sup> This work suggested the possibility that coronary artery thrombosis in man might, at times, be precipitated by spasm of these arteries. In order to throw some light on this problem we were interested in the possibility of producing thrombosis in the coronary arteries of the cat by the use of drugs that cause arterial spasm. Among the drugs used was epinephrine. We were impressed with the ability of epinephrine in suitable doses to produce in the electrocardiogram of the intact, unanesthetized cat S-T displacement similar to that seen in the most extreme changes of coronary occlusion. We are reporting these changes in this paper. They provide confirmatory evidence of the ability of epinephrine to produce spasm of the coronary arteries and seem to offer a simple test of the ability of various drugs to cause dilatation of these arteries.

## METHOD

From 1.5 to 2 c.c. of epinephrine 1:1000 (Armour) was injected into the thigh muscles of intact, unanesthetized cats. Control electrocardiograms were taken prior to treatment. Frequent electrocardiograms were taken after the administration of the epinephrine and, after marked S-T changes were produced, nitroglycerin gr.  $\frac{1}{50}$ , in aqueous solution, was injected into the opposite thigh muscle and further electrocardiographic studies made. Seventeen experiments were done, using eight cats.

In the normal electrocardiogram of the cat Lead I usually shows deflections that are almost isoelectric, and Leads II and III are very similar in appearance. For this reason transient changes were followed in Lead II, although all three leads were taken whenever time permitted.

Cambridge electrode jelly was used and lead electrodes were applied directly to the skin. The string was standardized to deflect 1.5 cm. to a millivolt.

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## RESULTS

Marked S-T displacement was obtained in all experiments and in many this displacement was so marked that the QRST curve was monophasic in type. In most experiments the S-T interval was depressed below the isoelectric line, but in some the change took place in the opposite direction. Two typical experiments are outlined below, one illustrating the production of marked S-T elevation and the other showing marked S-T depression.

Experiment No. 4, Nov. 2, 1936. Control electrocardiogram normal. One and one-half cubic centimeters of epinephrine 1:1000 was injected into the right

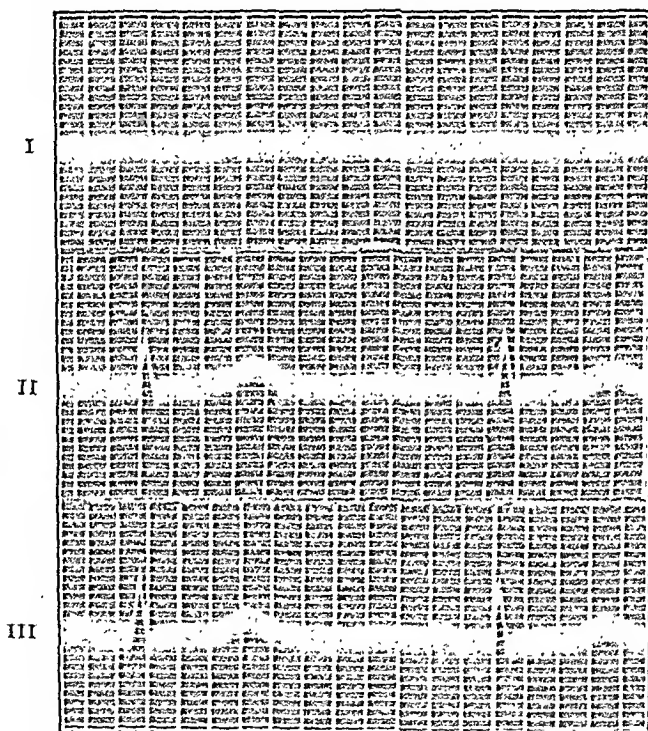


FIG. 1.—Experiment 4. November 2, 1936. Control electrocardiogram, Leads I, II, and III.

thigh muscles. An electrocardiogram taken at once showed slowing of the rate and then the production of a nodal rhythm. Five minutes after the administration of the epinephrine marked elevation of the S-T interval was found in all three standard leads, and in six minutes a monophasic curve was obtained (Figs. 1, 2, and 3). There was a rapid return of the displaced S-T segment toward the isoelectric line and in twelve minutes the segment was again isoelectric.

On Nov. 6, 1936, the same experiment was repeated with the same animal. Again marked elevation of the S-T interval was produced in five minutes, although not as marked as in the first experiment on this animal. The change persisted for twenty minutes.

On Nov. 13, 1936, the experiment was repeated a third time with the same animal. This time no S-T displacement was obtained.

Experiment No. 9, Dec. 5, 1936. Control electrocardiogram normal. One and one-half cubic centimeters of epinephrine 1:1000 was injected into the right thigh muscles. A tracing taken two minutes after the injection showed marked slowing. In five minutes S-T depression appeared and tracings taken at nine and nine and one-half minutes showed very marked depression of the S-T segment (Figs. 4, 5, and 6). At the ten-minute mark nitroglycerin, gr. 1/50, was injected into the left thigh

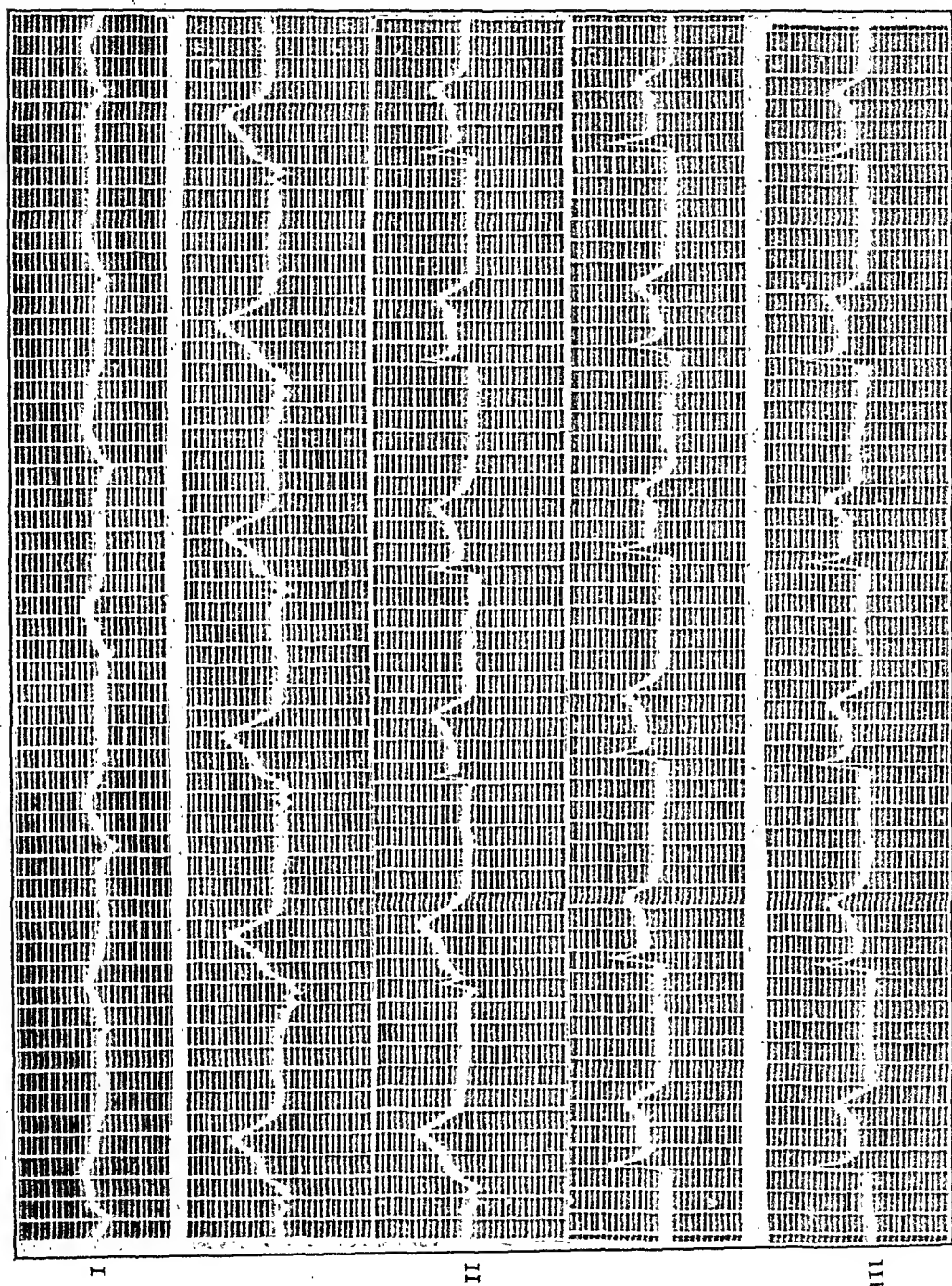


Fig. 2.—Experiment 4. Six minutes after injection of epinephrine. Lead I, Lead II—continuous strips — and Lead III.

muscles. A tracing taken as soon as possible after this treatment showed return of S-T to the isoelectric level, and the T-wave, which had been inverted, became upright. The effect of the nitroglycerin was very transient. One minute after its administration there was a return to a depressed S-T interval and an inverted T-wave and this type of curve continued for three and one-half minutes after which the S-T interval was isoelectric, although the inversion of T lasted for about twenty-five minutes.

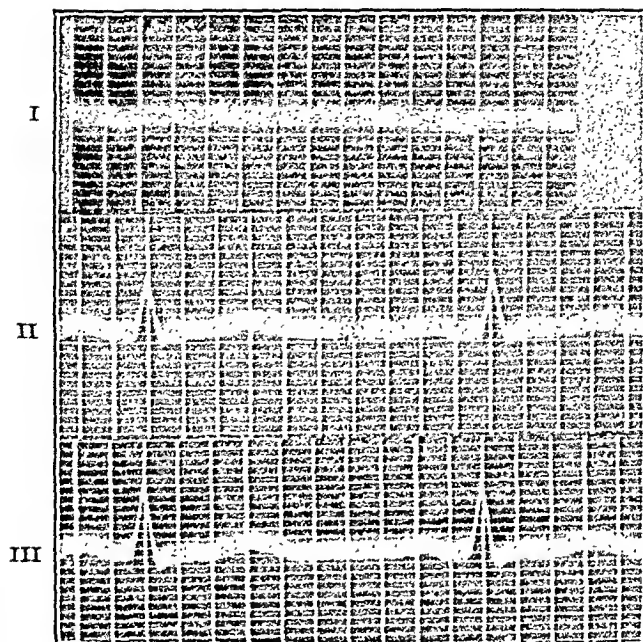


Fig. 3.—Experiment 4. Twenty-five minutes after injection of epinephrine showing return to normal, Leads I, II, and III.

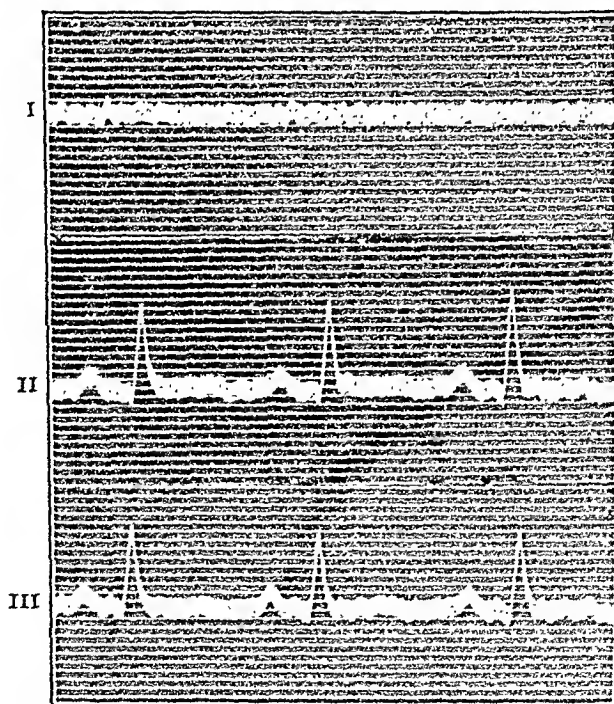


Fig. 4.—Experiment 9. Dec. 5, 1936. Control electrocardiogram, Leads I, II, and III.



## DISCUSSION

In 1920, Pardee<sup>2</sup> called attention to the S-T displacement in the electrocardiogram with acute coronary occlusion in man. Much experimental work has appeared since in which similar changes were produced in

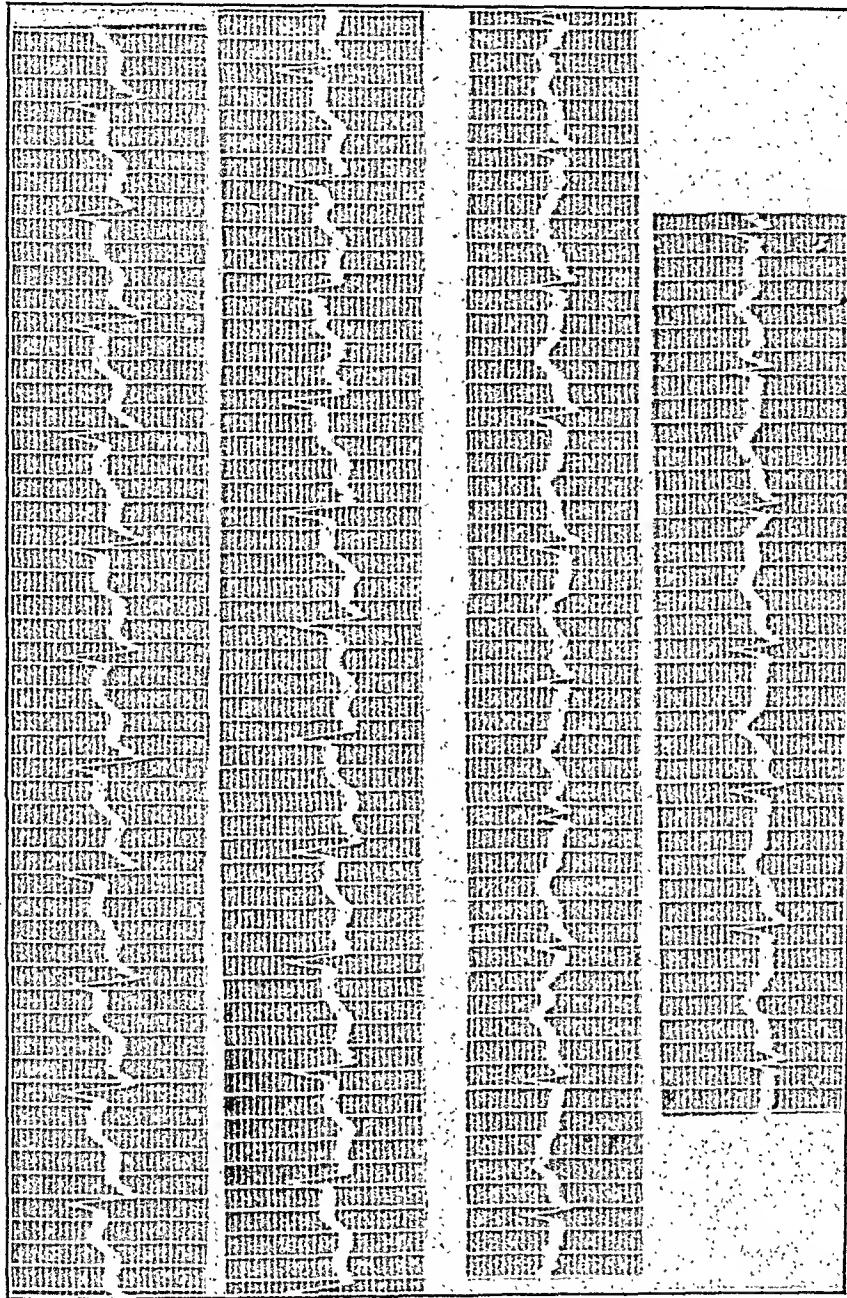


Fig. 5.—Experiment 9. A, Nine and one-half minutes after injection of epinephrine, Leads II and III; B, immediately after injection of nitroglycerin, about 10¼ minutes after epinephrine, Leads II and III.

animals. In most of this experimental work the heart was exposed and subjected to various mechanical, chemical, thermal, and electrical procedures.<sup>3</sup> In other experiments the same type of electrocardiographic curve was produced in the intact animal by anoxemia,<sup>4-7</sup> insulin,<sup>8</sup> digitalis,<sup>9</sup> and pitressin.<sup>10</sup> We show in this paper that epinephrine in suitable doses can produce similar changes; that these changes are consistently produced, unlike those caused by digitalis or insulin; and that



they are as marked as the changes reported by Kountz and Gruber<sup>10</sup> with pitressin in anoxemic dogs. As in the latter work the changes could be made to disappear by the administration of nitrites.

As Fig. 2 and 5 illustrate, the displacement of S-T produced by epinephrine can be above or below the isoelectric level, and can be marked

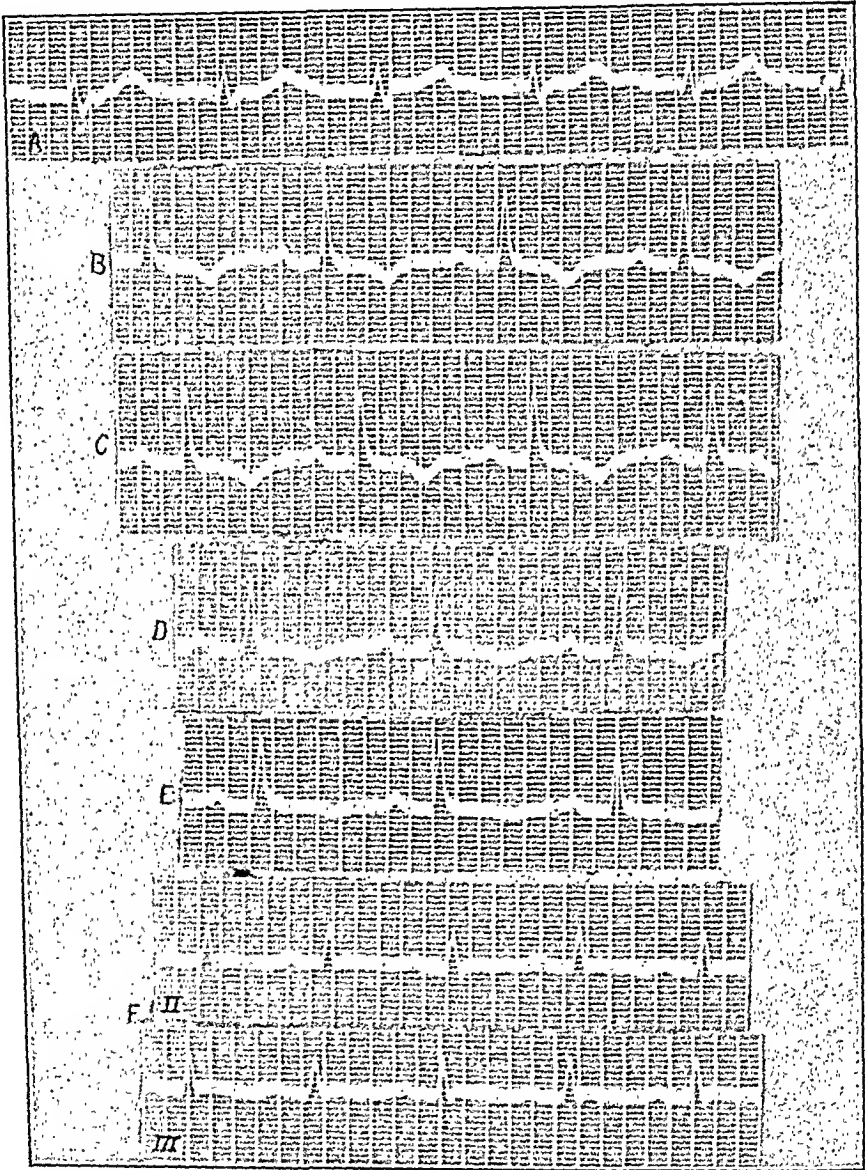


Fig. 6.—Experiment 9. A, Lead II taken one-half minute after injection of nitroglycerin; B, one minute later; C, two minutes after; D, ten minutes after; E, twenty-five minutes after; F, Leads II and III one hour after the injection of nitroglycerin.

enough to make the QRST curve monophasic. The fact that nitroglycerin can cause a quick but transient return to normal suggests that the changes are the result of spasm of the coronary arteries, probably secondary to stimulation of the sympathetic nerve endings that supply these vessels. In some experiments paroxysmal ventricular tachycardia

induced by epinephrine was quickly abolished by nitroglycerin. This suggests that coronary artery spasm is not only responsible for the S-T segment change but also plays a part in the initiation of arrhythmias.

The electrocardiographic effects of epinephrine in animals have been studied by a number of authors.<sup>12, 13</sup> These authors, however, used smaller doses than those injected in our experiments and emphasized disturbances in cardiac rate and rhythm. When S-T displacement was produced it was much less marked than the changes reported in this paper. In the present study we have been interested primarily in the action of epinephrine on the S-T segment and the coronary arteries. That the drug has, in addition, a direct action on the sympathetic nerve endings in the heart apart from the coronary arteries, and an indirect, reflex action from the hypertension it causes, has been demonstrated by others.<sup>11, 12</sup>

The effect of epinephrine on the electrocardiogram has been studied in man as well as in animals. Anginal seizures and S-T displacement have been produced<sup>7, 14-16</sup> but the S-T changes were slight, probably because the doses used were necessarily small.

In addition to electrocardiographic studies many direct investigations have been made of the action of epinephrine on the coronary arteries and the coronary circulation. The earlier work has been reviewed by Gruber and Roberts.<sup>17</sup> These authors worked on the perfused, excised hearts of cats, rabbits, and rats and concluded that the drug in dilute solutions causes vasodilatation, and in concentrated solutions, vasoconstriction. Our findings are consistent with these conclusions and add further evidence to support the view that epinephrine can cause marked coronary artery spasm.

We believe that the S-T displacement caused by epinephrine in the electrocardiogram of the cat might be used as the basis for a simple test of the ability of other drugs—e.g., theobromine or theophylline—to relieve coronary artery spasm. The changes are conspicuous, and can be consistently and easily produced.

#### CONCLUSIONS

1. Epinephrine in suitable doses can produce marked displacement of the S-T segment of the electrocardiogram of the cat. This displacement can be above or below the isoelectric level. It can be so marked that a monophasic curve results.

2. The S-T changes produced by epinephrine can be abolished by nitroglycerin.

3. These changes are probably the result of coronary artery spasm.

4. They can be used as a basis for testing the ability of drugs to relieve coronary artery spasm.

## REFERENCES

1. Lewis, Thos.; in collaboration with B. Gelfand: The Manner in Which Necrosis Arises in the Fowl's Comb Under Ergot Poisoning, *Clin. Sc.* 2: 43, 1935.
2. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, *Arch. Int. Med.* 26: 244, 1920.
3. Crawford, J. H., Roberts, G. H., Abramson, D. L., and Cardwell, J. C.: Localization of Experimental Ventricular Lesions by the Electrocardiogram, *AM. HEART J.* 7: 627, 1932.
4. Kountz, W. B., and Gruber, C. M.: The Electrocardiographic Changes in Anoxemia, *Proc. Soc. Exper. Biol. & Med.* 27: 170, 1929.
5. Kountz, W. B., and Hammouda, M.: Effect of Asphyxia and Anoxemia on the Electrocardiogram, *AM. HEART J.* 8: 259, 1932.
6. Katz, L. N., Hamburger, W. W., and Schutz, W. J.: Effect of Generalized Anoxemia on the Electrocardiogram of Normal Subjects, *AM. HEART J.* 9: 771, 1934.
7. Rothschild, M. A., and Kissin, M.: Induced General Anoxemia Causing S-T Deviation in the Electrocardiogram, *AM. HEART J.* 8: 45, 1933.
8. Edwards, D. J., and Page, I. H.: Observations on the Circulation During Hypoglycemia From Large Doses of Insulin, *Am. J. Physiol.* 69: 177, 1924.
9. De Graff, A. C., and Wible, C. L.: Production by Digitalis of T-Wave Changes Similar to Those of Coronary Occlusion, *Proc. Soc. Exper. Biol. & Med.* 24: 1, 1926.
10. Gruber, C. M., and Kountz, W. B.: Effect of Pitressin on Heart, *Proc. Soc. Exper. Biol. & Med.* 27: 161, 1929.
11. Gruber, Chas. M.: A Note on the Effect of Epinephrine on the Excised Terrapin Sino-Auricular and Auricular Apex Strips, *J. Pharmacol. & Exper. Therap.* 52: 23, 1934.
12. Hoff, H. E., and Nahum, L. H.: The Role of Adrenaline in the Production of Ventricular Rhythms and Their Suppression by Acetyl-B-Methylcholine Chloride, *J. Pharmacol. & Exper. Therap.* 52: 235, 1934.
13. Whitehead, R. W., and Elliott, D. C.: Electrocardiographic Studies of the Action of Alpha Lobeline and Epinephrine on Mammalian Heart, *J. Pharmacol. & Exper. Therap.* 31: 145, 1927.
14. Rothschild, M. A., and Kissin, M.: Production of Anginal Syndrome by Induced General Anoxemia, *AM. HEART J.* 8: 729, 1933.
15. Levine, S. A., Ernstene, A. C., and Jacobson, B. M.: The Use of Epinephrine as a Diagnostic Test for Angina Pectoris, *Arch. Int. Med.* 45: 191, 1930.
16. Katz, L. N., Hamburger, W. W., and Lev, M.: Diagnostic Value of Epinephrine in Angina Pectoris, *AM. HEART J.* 7: 371, 1932.
17. Gruber, C. M., and Roberts, S. J.: Effect of Adrenalin on the Coronary Circulation, *Am. J. Physiol.* 76: 508, 1926.

# ANOMALOUS ORIGIN AND COURSE OF THE LEFT CORONARY ARTERY IN A CHILD

## SO-CALLED CONGENITAL ABSENCE OF THE LEFT CORONARY ARTERY\*

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THE type of anomaly here reported usually appears in the literature under the title of congenital absence of the left or right coronary artery. All authors recognize the fact, however, that the essential lesion consists not of an absence of the vascular supply, ordinarily provided by the coronary artery in question, but of an abnormality of its origin, course, and distribution.

Upon examination, the reputedly absent coronary artery cannot be found running from the aorta in normal position; its orifice is completely lacking. In one group of cases the artery arises—either in itself or in its branches—along with or from the homologous coronary vessel. In a second group anatomical counterparts of the absent artery are not distinguishable as such. Then the coronary artery which is considered to be present gives off branches and terminations that act as functional substitutes. Because of the anomalies in origin, the components of the coronary circulation also assume variations in caliber and course.

### REVIEW OF LITERATURE

References to the anomalous origin and course of the coronary artery here presented, as an isolated cardiac defect are rather few. Mention is made of it in the classical literature by Galen, Bartholinus, Fantonus, Morgagni, and Thebesius. In their works Otto, Cruveilhier, Gegenbauer, Kaufmann, Maude Abbott,<sup>1</sup> and Bland, White and Garland<sup>2</sup> offer brief citations. During the past one hundred years complete descriptions of only eleven cases have appeared in the medical journals; two of these are recorded in the American literature.

In Hyrtl's case<sup>3</sup> (1841) the subject was a seven-month fetus. The right coronary artery was missing; it was replaced by branches from the left coronary artery.

In Buehdalek's case<sup>4</sup> (1867) the patient was a sixty-year old woman. The cause of death was not given. The left coronary artery was anomalous. A single artery sprang from the right sinus of Valsalva and soon divided into three branches. One of these corresponded to the normal right coronary artery. The second passed between the aortic root and left auricle and took the place of the left circumflex branch. The third branch traversed a path to the left, through the

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muscle of the posterior wall of the left ventricle and interventricular septum, and came out on the surface as the left anterior descending artery. Histological sections were not described.

In Engelman's case<sup>5</sup> (1898) the age and the sex of the patient and the cause of death were not tabulated. The right coronary artery was abnormal. A single artery originated behind the left anterior cusp. It broke shortly into a vertical and horizontal branch. The former ran anteriorly and gave off a small branch which passed to the right between the pulmonary artery and the aorta to the posterior surface of the heart and an abnormally large branch to the anterior wall, margo aëutus, and the posterior wall of the right ventricle. The horizontal branch followed the course of the left circumflex vessel. Histological descriptions were not included.

In Plaut's case<sup>6</sup> (1922) the patient was a thirty-seven-year-old man. He suffered primarily from subacute bacterial endocarditis. The right coronary artery was called absent. In the right sinus of Valsalva only a small dimple could be seen. The left coronary arose at the normal site. The circumflex branch ran in the sulcus atrioventricularis of the whole heart and ended in a small branch 3 cm. from the usual origin of the right coronary artery. Along its course this artery gave off three branches to the left, and three small branches to the right anterior cavity, and numerous branches to the posterior surface of the heart. Twelve centimeters from the origin of the left anterior descending artery, a large branch proceeded down to the right to both surfaces of the right heart. The anomaly was not connected with the cause of death. Histological descriptions were not given.

In the case of Gallavardin and Ravault<sup>7</sup> (1925) the patient was a forty-five-year-old woman who was afflicted with chronic mitral and aortic endocarditis. The left coronary artery was anomalous. The aorta presented one coronary orifice in the right sinus. From a small common trunk passed a normal right coronary artery and a second vessel which sank into the ventricle between the pulmonary conus and the right auricle to emerge and to divide into a left descending and a circumflex branch. The last was not entirely normal and formed two branches. The anomaly did not figure in the death of the patient. Histological sections of the myocardium were not described.

In the case of Smith and Graber<sup>8</sup> (1926) the patient was a forty-six-year-old man. Death was caused by coronary thrombosis. The left coronary artery was called absent. There was only one coronary orifice in the right anterior sinus. The artery leading from this opening was large and followed the usual course of the right coronary artery. Posteriorly it divided into two branches. The larger descended along the interventricular septum, where it was found thrombosed. The smaller continued around the atrioventricular groove to the margin and the apex of the left heart to pass upward on the anterior

surface. Here it joined a large artery coming down over the base of the right ventricle from the first portion of the main coronary artery, which continued to the posterolateral aspect of the left ventricle. The thrombotic lesion in the anomalous coronary circulation produced death. Microscopically the myocardium showed fibrosis.

In Gratzner's case<sup>9</sup> (1926) the patient was a sixty-eight-year-old woman. She died from thrombophlebitis of the veins of the legs, and pulmonary infarcts. The heart showed myomalacia, parietal thrombosis, and aneurysm of the wall. The left coronary was anomalous. Three orifices were seen in the right sinus of Valsalva. The middle opening gave off the largest vessel, which traveled through the right atrio-ventricular sulcus to the posterior wall of the right ventricle, distributed a branch to the posterior sulcus and continued to the left heart. From the left ostium there arose a vessel which supplied the anterior part of the left ventricle and the apex. From the right ostium a vessel was traced to the right anterior heart. The anomaly apparently did not figure in the cause of death. Histological sections were not described.

In Petren's case<sup>10</sup> (1930) the patient was a thirty-three-year-old man. Death was attributed to hypertension and cerebral hemorrhage. The right coronary artery was abnormal. The left coronary artery arose from a large opening and divided into anterior and circumflex branches. At the apex the anterior descending artery turned to the right ventricle. The circumflex branch crossed posteriorly and gave off descending branches to the left ventricle, the posterior sulcus, and the right ventricle. Death was not connected with the anomalous vessel. Histological descriptions were not included.

In Kintner's case<sup>11</sup> (1931) the patient was a sixty-five-year-old man. Death was caused by renal insufficiency and pulmonary embolism. The left coronary artery was anomalous. The right coronary orifice was larger than normal and served as a common opening for two vessels. The larger of these went through the right coronary sulcus to the posterior heart. A small artery passed from the common orifice down to the left at the root of the aorta beneath the muscle of the posterior wall, then through the interventricular septum. It finally reached the anterior surface of heart and divided into left ascending and descending arteries. The former replaced the left circumflex branch; the latter, the left anterior descending branch. The anomaly played no part in the cause of death. Histological descriptions were not given.

In Born's case<sup>12</sup> (1933) the patient was a fifty-four-year-old man. The primary cause of death was empyema and pulmonary gangrene. The left coronary artery was absent. From a common opening issued the left and right coronary arteries. The first ran between the aorta and the conus pulmonalis into the septum and emerged to give off the left descending and circumflex branches. The right coronary artery helped supply the left ventricle posteriorly. Death was not associated with the anomaly. Sections were not described.

In Koekel's case<sup>13</sup> (1934) the patient was a thirty-nine-year-old woman. She died of pneumonia and pericarditis. The right coronary artery was anomalous. The left coronary artery divided into left anterior descending and left circumflex vessels. These provided branches to anterior and posterior parts of the right heart. The anomaly played no part in the cause of death. No histological description was given.\*

#### REPORT OF CASE

*History.*—J. B., a white American male child, aged three years and ten months, was admitted to the Buffalo Children's Hospital on Aug. 21, 1936, because of generalized edema of several days' duration. He died within two days.

The father and mother, each 33 years of age, were in good health. The patient was the last of five children. He was born at full term. Delivery was spontaneous and uneventful. At birth the child did not emit a cry but seemed to breathe normally. There was no cyanosis. Immediately after birth bilateral strabismus was noted. Our patient was breast fed for nine months. He had received no cod liver oil or orange juice. He had never talked or walked, though he climbed nimbly. Immunization for diphtheria had been carried out. Except for occasional colds, the past history was negative.

Several days before hospital entry, the patient became listless. Edema was noted by the mother. The urine was scanty and highly colored.

*Examination.*—The temperature was 100° F.; pulse, 120; and respiratory rate, 28. The weight was 27 pounds. The child was well developed and well nourished but pale. He showed generalized pitting edema. The biparietal diameter of the skull was narrow; the fronto-occipital diameter, long. Bilateral internal strabismus was present. Pinpoint hemorrhages were noted in the fundi. Both nares contained dried blood. The tonsils were large. The lungs were apparently clear. The heart was not enlarged. The blood pressure was 70 systolic and 30 diastolic. The right testicle was undescended. Deep reflexes were hypoactive. Examination of the urine was negative. The clinical impression was acute glomerulonephritis and chronic tonsillitis.

#### AUTOPSY FINDINGS

The autopsy was made eight hours after death. The final diagnosis comprised acute diffuse glomerulonephritis; marked edema and congestion of both lungs, with patchy areas of atelectasis of the lower lobes; slight bilateral hydrothorax; slight hydropericardium; slight ascites; edema of the soft tissues; diffuse myocarditis; acute interstitial hepatitis; recent interstitial myositis (diaphragm); acute splenitis; congestion of the brain; anomalous origin and course of the left coronary artery; anomalous course of the right coronary artery; synostosis of the skull; bilateral strabismus. The line of ossification was regular. No lesions were found in the stomach or the intestines. Peripheral nerves were examined.

*Description of the Heart.*—On removal of the sternum, the pericardium was found slightly distended. The pericardial fluid was straw colored and slightly increased in amount. The longitudinal diameter of the heart measured 7 cm.; the horizontal diameter at the atrioventricular sulcus, 7 cm. The weight was 60 gm. The apex was somewhat rounded. The epicardial fat was normal in amount. The vessels on the surface of the heart were very prominent and tortuous.

The aortic cusps were three in number. They showed no vegetation. That of the right anterior sinus was slightly fenestrated. No coronary orifice was seen in the

\*In a forty-year-old woman who died from malignant hemangioma, Hall<sup>14</sup> noted that the right coronary artery had no opening into the aorta but that the artery was found in epicardial fat about 1 cm. from the aorta.

left anterior sinus. A shallow dimple—pinhead sized—was present in the anterior sinus close to the commissure between both anterior sinuses. This dimple was not in the position of the normal origin of the left coronary artery. In the right sinus of Valsalva was situated a large orifice 0.25 cm. in diameter. When it was stretched, the large orifice revealed three moderate-sized openings and one very minute

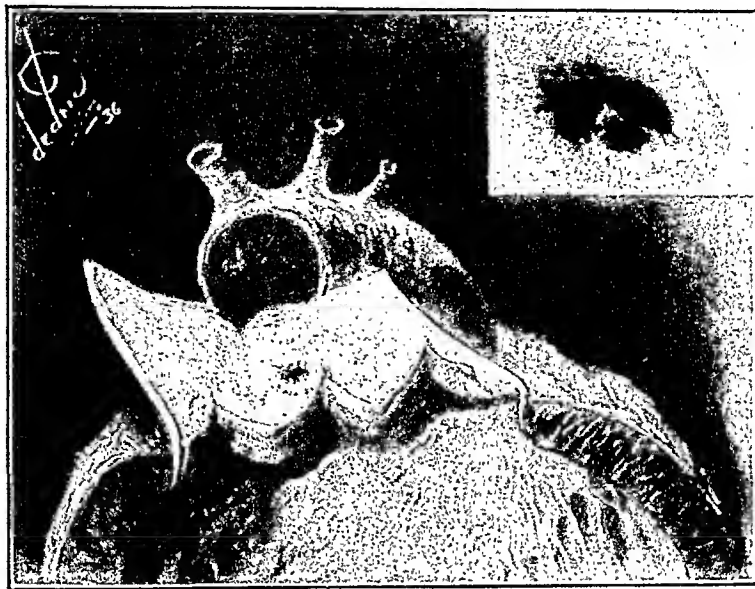


Fig. 1.—Gross view of aorta showing common coronary orifice in right anterior sinus. Inset depicts magnified common orifice and adjacent minute opening.

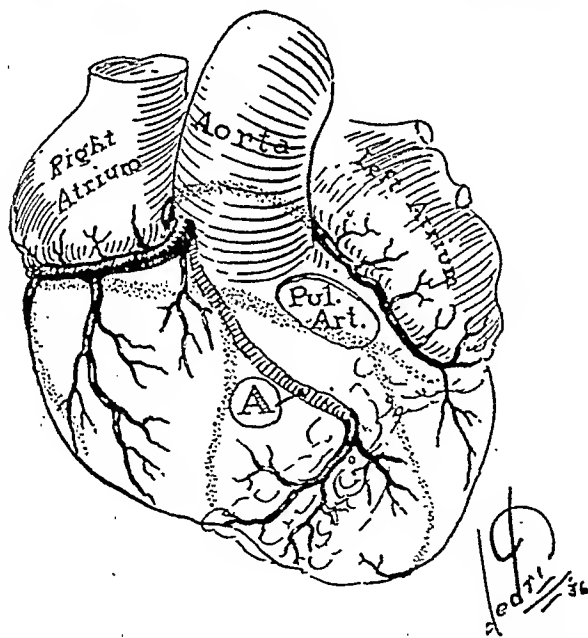


Fig. 2.—Diagram of course and distribution of coronary arteries. A, left descending branch passing through the interventricular septum. Stippling indicates continuation of arteries on the posterior surface of the heart.

opening. The moderate sized openings were arranged so that two occupied a superior position, and one a site midinferior to the upper two. The minute opening lay between the right superior and midinferior orifices. An additional minute opening was noted in right sinus just medial to large orifice. From the right superior opening emerged a vessel which corresponded to the right coronary artery. It measured 0.3 cm. in circumference. Three large branches to the right anterior



ventricle, a large branch to the margo acutus, and small branches to the right atrium were given off. Traveling in the atrioventricular sulcus, the vessel, interpreted as the right coronary artery, continued beyond the margo acutus to the posterior part of right ventricle. Here it distributed a large branch to the posterior descending sulcus. The vessel was next traced (still in the atrioventricular sulcus) for a distance of 2 cm. on to the posterior wall of the left ventricle. A large branch passed downward and diagonally to margo obtusus, and thence to the antero-inferior part of the left ventricle. The main right coronary artery was followed another centimeter in atrioventricular sulcus; it terminated at margo obtusus. The right coronary artery measured 10 cm. in length.

The left superior opening in the right anterior sinus gave origin to a vessel that sank into septum between pulmonary artery and aorta and penetrated downward for a distance of 1 cm. At this point it made a 125-degree-angle turn toward the anterior surface of the heart. After 1 cm. the artery reached the subepicardium at the interventricular sulcus 2.2 cm. from the aortic ring. On the surface of the heart, it conformed to the topography of the left anterior descending branch for 3 cm. and supplied both the left and the right ventricles.

From the midinferior opening a vessel passed behind the posterior and left aortic cusps to the left. It came out in the left interventricular sulcus at junction of anterior mitral leaflet and the left aortic cusp. This artery was 4 cm. in length and corresponded in part to the left circumflex branch. It gave off small branches to the anterior part of the left ventricle and the margo obtusus.

The two minute openings in the right anterior sinus could not be probed or dissected because of their size. The veins of the heart were not remarkable. The superior and inferior venae cavae were not remarkable.

The right auricular appendage contained no thrombi. The wall of the right atrium measured 0.08 cm. The tricuspid valve was thin and delicate. It measured 0.5 cm. in circumference. The wall of right ventricle was 0.3 cm. thick. The cavity measured 5.8 cm. The chordae tendineae and the papillary muscles were not remarkable. The pulmonary artery was free. It measured 4 cm. above the valve. Pulmonic cusps showed slight fenestration. The pulmonary veins were patent. The foramen ovale was closed. The left auricular appendage was clear. The endocardium of the posterior wall of the right atrium showed few white ridges. The wall measured 0.18 cm. The mitral valve was 5 cm. in circumference. The anterior leaflet showed an atheromatous patch 0.2 cm. in diameter. The wall of left ventricle measured 0.5 cm.; the cavity, 5 cm. The aorta measured 3 cm. above the valve.

On section the color of the myocardium of the left ventricle especially of its posterior wall was pale. Scattered throughout were small gray patches and streaks. Dilated vessels and petechial hemorrhages were also seen.

*Microscopic Findings.*—Blocks of tissue were taken from various parts of ventricles and atria and fixed in 10 per cent formaldehyde. Frozen and paraffin sections were made and stained with hematoxylin-eosin, van Gieson, Weigert elastic, Gram-Weigert, sudan III, methyl green-pyronine, and Levaditi methods. Studies of the sections revealed that changes were present in both ventricles. The findings were most marked in the left ventricle and in the posterior wall of the left ventricle. The histological picture included a distinct recent diffuse interstitial myocarditis, parenchymatous degeneration and atrophy of myocardial fibers, dilatation of capillaries, recent interstitial hemorrhages, and epicarditis.

The lesion in the left ventricle will be described. The endocardium was normal in thickness. Fibrosis and elastification could not be made out. No thrombi were seen on the surface. Throughout the wall distinctly atrophic fibers could be distinguished between those of normal size.

At first glance the three myocardial zones appeared to take the hematoxylin-eosin stain evenly. However, upon tracing the course of individual fibers, one noted

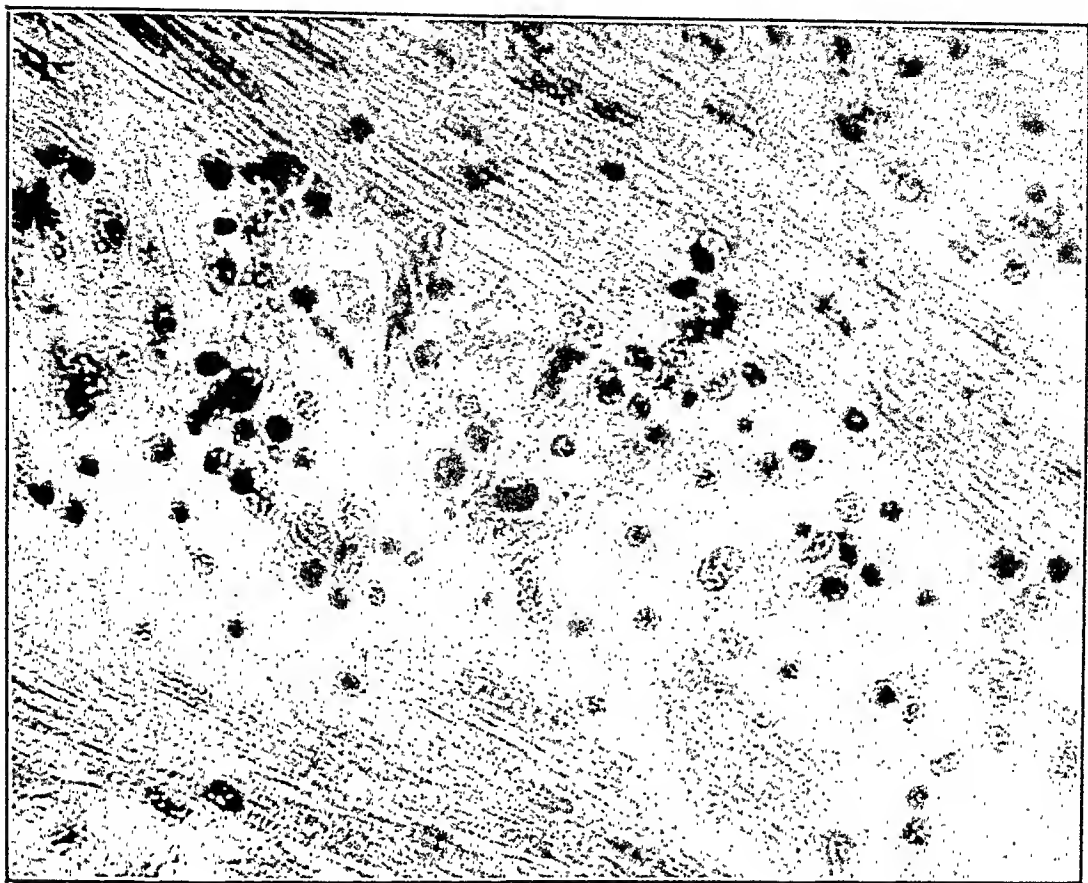


Fig. 3.—Section of myocardium showing interstitial edema and cellular infiltration.

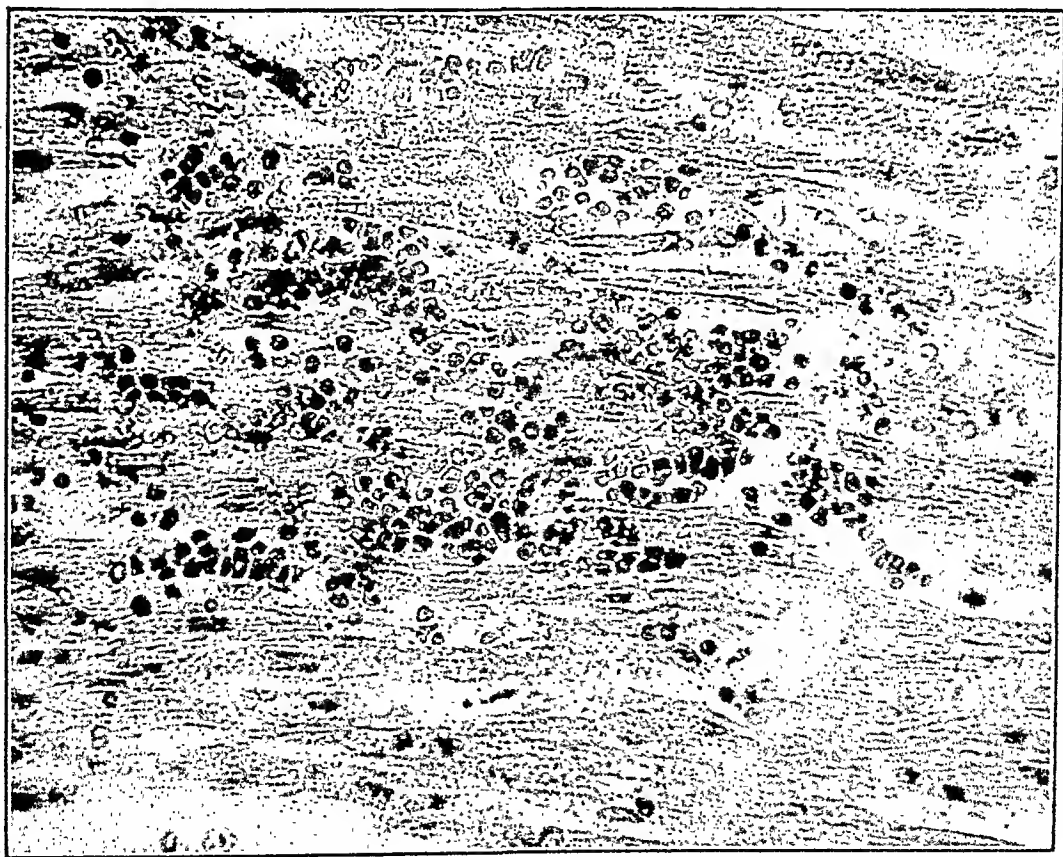


Fig. 4.—Section of myocardium showing injected capillaries and recent interstitial hemorrhages.

that areas which took a pale stain were scattered along intensely pink-staining fibers. Under high power the pale areas showed loss of striations and frayed fibrillae. In the outer zone of myocardium vacuoles were present in sarcoplasm. Nuclei were pale—oval or rectangular in shape; chromatin material was not prominent. In some pale areas the muscle fibers had disappeared with formation of gaps. In others the sarcolemma alone was preserved. Sudan stain revealed fatty degeneration in patchy distribution.

The most striking variations from normal in the myocardium were observed not in the muscle fibers themselves, but in interstitial spaces and in the gaps mentioned above. Muscle fibers were separated by edema. Capillaries were dilated. In the interstitial spaces and gaps were neutrophiles, eosinophiles, round cells, mast cells, and plasma cells. There were marked proliferations of fixed tissue cells. These appeared as oval cells with vesicular nuclei. Few macrophages had indented or double nuclei. The cellular infiltration was found in all zones. The areas of infiltration in different sections ran parallel to muscle fibers and in perpendicular zigzag courses. With the van Gieson stain thin collagenous fibrillae were noted running in interstitial spaces. The perivascular tissue about the moderate sized coronary arteries showed edema and infiltration of neutrophiles and plasma cells, and proliferation of histiocytes. Often around the vessels there was a halo of edema. No distinct nodular arrangement was seen. The branches of the coronary arteries were patent.

The subepicardial tissue showed cellular infiltration and histiocytic proliferation. These changes reached in between the muscle fibers of the outer muscle zone. In certain sections recent interstitial hemorrhage had occurred in the myocardium. The endocardium of the mitral and the aortic valves was not remarkable. Bacteria were not found.

#### DISCUSSION

Discussion of the case just described will be concerned for the most part with two questions. In what respects does our case contribute to the knowledge of anomalous origin and course (so-called congenital absence) of either coronary artery? What explanations have been proffered for occurrence of the anomaly?

In our case the coronary arteries arise in the right anterior aortic sinus from a common orifice which houses three moderate sized openings and one minute opening, and from one separate minute opening. This type of origin is not duplicated among the eleven reported examples of anomalous left or right coronary artery.

The distribution of branches of the coronary arteries in our case, however, corresponds to the findings of other authors in certain cases of anomalous coronary artery. In fact, these cases, by a characteristic distribution of vessels, form a distinct group—that of anomalous left artery. In this group the left anterior descending branch arises separately or from right coronary artery, penetrates the interventricular septum, and emerges on the anterior wall of left ventricle. The left circumflex branch passes between the aortic root and the left auricle to reach the atrioventricular sulcus. In a second group of anomalous left coronary artery, the left circumflex branch is absent or rudimentary. In both groups the right coronary artery gives off branches to the left ventricle.

Reported cases of anomalous right coronary artery also follow a uniform vascular distribution. The left artery divides into a left anterior descending and a circumflex branch. These supply vessels to anterior and posterior parts of right heart.

Cognizance of the classification of anomalous coronary artery on the basis of vascular distribution, which is formulated here for the first time, ought to preclude further arguments on the nosological question: Is it proper to term the anomalous artery absent or not? In the anomalous left coronary artery, exemplified by our case, the abnormal vessel—from a strict anatomicophysiological sense—cannot be said to be absent. The developmental defect lies in an absence of its orifice at the customary site in the aorta and in the abnormality of its branches and course. Branches corresponding to those of the ordinary left coronary artery are present; in addition, branches from the right coronary artery supply the left ventricle.

On the other hand, cases of anomalous right coronary artery, from an anatomical point of view, may be justifiably called instances of congenital absence of the right coronary artery. Counterparts of branches of the right coronary artery are not manifest.

Our case is the first instance of so-called congenital absence of the coronary artery to be discovered in a child. This fact is important because in a child's heart we are able to study the possible effects of the anomalous coronary artery on the myocardium without having to take into account cardiac lesions of adult life, such as coronary arteriosclerosis.

Histological description of the myocardium occurs in but one recorded case of anomalous origin and course of the coronary artery (Smith and Graber). Here, any causative relation of the anomalous coronary artery is hard to evaluate, for the microscopic changes can be explained by a coronary thrombosis; the effects of the anomalous vessel, if present at all, are completely overshadowed by the superimposed vascular obturation.

In our case distinct histopathological findings are noted in the myocardium. Indeed, these could already be detected grossly. The myocardial damage consists chiefly of a recent diffuse myocarditis, interstitial and parenchymatous in type, capillary dilatation, and recent hemorrhages. The problem of the etiology and pathogenesis of this damage must be faced. Are the lesions due to an alteration in blood supply brought about by the anomaly? Or are they dependent on an unrelated etiological factor? Is the combination of such a factor with the coronary anomaly merely a coincidence? Or may the anomaly predispose the myocardium to the deleterious action of another pathogenic agent?

Claims have been made that the portions of the heart supplied by the anomalous coronary artery receive a diminished circulation. Physiological substantiation for this belief has never appeared. It is

true, however, that the branches of the anomalous vessel are not of usual length; their caliber tends to be small. Though the artery which is considered to be present assumes added function, it does this through secondary or end branches. None of the hearts in the literature has been studied radiographically for the extent of anastomoses. But in infants and children coronary anastomoses are normally least developed; the left ventricle possesses normally a lesser blood supply than the right. Yet, to our mind the explanation for the myocardial changes in our case solely on the assumption of diminished blood supply and diminished oxygen supply attendant upon the anomaly, is not completely satisfying. The myocardial changes are recent; the inflammatory lesion is most prominent; scarring as from coronary insufficiency, either mechanical or functional in origin, is not seen.

In a search for primary etiological and pathogenic factors besides the coronary anomaly, we can rule out syphilis, severe anemia, myxedema, embolism, von Gierke's disease, rheumatic fever, beriberi, and bacterial myocarditis. Toxic or infectious-toxic myocarditis must be considered first. Interstitial myocarditis has been described in uremia. Our patient died from acute glomerulonephritis. Blood chemistry determinations for urea nitrogen were not carried out *intra vitam*. On an infectious-toxic basis, the cardiac lesion could fit in with changes in kidney, liver, muscle, and spleen.

It is difficult to say how far the effects, if any, of the anomalous coronary artery increased the susceptibility of the myocardium to the action of some toxin. We must note that the left ventricle and its posterior wall, which would suffer the consequences of the anomalous blood supply, are apparently most involved in the myocardial lesion. (But myocarditis can attack one side of the heart to a greater degree than the other.) Muscle fibers show atrophy and fatty degeneration. When we realize, however, that ours is the first case of so-called congenital absence of coronary artery reported with adequate histological studies, we believe it is safest to record our findings without drawing categorical conclusions. Microscopic descriptions in future cases may help to decide whether the anomalous coronary artery produces any primary or predisposing effects and whether the myocardial damage in our case is only an accident.

Plaut<sup>6</sup> sought an explanation for the "absence" of the coronary artery on embryological and phylogenetic grounds. Embryology offered little clarification. The first anlage of the coronary arteries in the rabbit appears as a thickening in the aortic endothelium from the twelfth to fourteenth days of embryonic life and just before truncus arteriosus has been divided into aorta and pulmonary artery. The left coronary artery is formed first. In the beginning the arterial rudiments are solid columns of cells which later acquire a lumen and grow outward into the superficial portion of the myocardium.<sup>2</sup>

In comparative anatomy Plaut found an interesting implication. In fish and amphibia there is only one coronary artery. In chelonidae and sauridae the number is often reduced to one or increased to three. Only 60 per cent of the birds have two vessels. Mammals as a rule show two coronary arteries. The development of two coronary arteries seems to be a late acquisition in the evolutionary process, associated with separation of heart chambers.

Before the diagnosis of so-called congenital absence of the coronary artery is ventured, origin from the pulmonary artery or from a position high in the aorta must be looked for. Complete occlusion of one coronary orifice by syphilis or arterosclerosis should be excluded. So-called congenital absence of the coronary artery is sometimes associated with other major cardiac anomalies.<sup>15</sup>

#### SUMMARY

The literature on so-called congenital absence of coronary artery as an isolated anomaly is reviewed. A case which illustrates this anomaly of the left coronary artery in a four-year-old boy is reported. Findings of unique significance include the type of origin of coronary arteries, the age of the patient, and the pathological changes in the myocardium.

#### REFERENCES

1. Abbott, Maude: Congenital Cardiac Disease, in William Osler and Thomas McCrae, *Modern Medicine*, ed. 3, Philadelphia, 1927, Lea and Febiger, vol. 14, p. 794.
2. Bland, E. F., White, P. D., and Garland, J.: Congenital Anomalies of Coronary Arteries: Report of Unusual Case Associated With Cardiac Hypertrophy, *AM. HEART J.* 8: 787, 1933.
3. Hyrtl: *Med. Jahrb. d. k. k. österr. Staats* 24: 25, 1841. Cited by Plaut and Petren.
4. Buchdalek, H.: Anormaler Verlauf der Kranzarterien des Herzens, *Virchows Arch. f. path. Anat.* 41: 260, 1867.
5. Engelmann, G.: Ein Fall von Mangel einer Coronarterie, *Anat. Anz.* 14: 348, 1898.
6. Plaut, A.: Versorgung des Herzens durch nur eine Kranzarterie, *Frankfurt Ztschr. f. Path.* 27: 84, 1922.
7. Gallavardin, L., and Ravault, P.: Anomalie d'origine de la coronaire antérieure, *Lyon méd.* 136: 270, 1925.
8. Smith, F. M., and Graber, V. C.: Coronary Thrombosis With Congenital Absence of the Left Coronary Artery, *Arch. Int. Med.* 38: 222, 1926.
9. Gratzner, A.: Der Seitenbahn Kreiskauf an einem Herzen mit einer Kranzschlagader, *Virchows Arch. f. path. Anat.* 262: 608, 1926.
10. Petren, T.: Ein Fall von Mangel der A. coronaria cordis dextra, *Virchows Arch. f. path. Anat.* 278: 158, 1930. Cited herein are Galen, Bartholinus, Fantonus, Morgagni, Thebesius, Otto, Cruveilhier, Gegenbauer, and Kaufmann.
11. Kintner, A. R.: Anomalous Origin and Course of Left Coronary Artery, *Arch. Path.* 12: 586, 1931.
12. Born, E.: Ueber Missbildungen der Kranzarterien und ihre Beziehungen zu Zirkulationsstörungen und plötzlichen Tod, *Virchows Arch. für path. Anat.* 290: 688, 1933.
13. Koekel, H.: Eigenartige Kranzschlagadermissbildungen, *Beitr. z. path. Anat. u. z. allg. Path.* 94: 220, 1934.
14. Hall, Ernest M.: A Malignant Hemangioma of the Lung With Multiple Metastases, *Am. J. Path.* 11: 343, 1935.
15. Ngai, S. K.: Congenital Anomalies of the Heart, *Am. J. Path.* 11: 309, 1935.

## APPARENT INCREASED VELOCITY OF BLOOD FLOW IN CASES OF CONGENITAL HEART DISEASE WITH SEPTAL DEFECTS HAVING RIGHT-TO-LEFT SHUNT\*

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WHILE engaged in a study of the hemodynamics of morbus caeruleus we noted an extreme "acceleration" of blood flow in a patient exhibiting the clinical syndrome associated with tetralogy of Fallot\* (patent interventricular septal defect, right ventricular hypertrophy, pulmonary stenosis, and dextroposition of the aorta). It occurred to us that this remarkable "acceleration" in velocity was apparent rather than real and was dependent upon a "short circuiting" through the patent interventricular septum. It is obvious that if this be correct a simple diagnostic test for septal defects with right-to-left shunt would be available.

The arm-to-carotid sinus circulation time was measured by the sodium cyanide method of Robb and Weiss.<sup>1</sup> This simple test consists of the rapid injecting of a 2 per cent solution of sodium cyanide into an antecubital vein and observing the time of the appearance of a sudden deep inspiration. The amount of cyanide given is determined on the basis of 0.11 mg. for each kg. of body weight. The test ordinarily measures the time necessary for blood to pass from the antecubital vein, through the right heart to the lungs, plus the time of passage through the lungs and the left heart to the carotid sinus. Robb and Weiss have shown that in the healthy adults the average arm-to-carotid circulation time is 15.1 seconds, the maximum time being 20 seconds, the minimum, 10 seconds. Likewise they showed that the time necessary for the cyanide to pass from the antecubital vein to the lung in normal adults (the venous velocity) averaged 4.5 seconds, while the crude pulmonary circulation time was 10.6 seconds.

The reaction taken as the end point in children was very definite and clear cut. The optimal reactive dose was found to be 0.13 mg./kg. for children as contrasted to the value of 0.11 mg./kg. obtained by Robb and Weiss for normal adults.

As no reported studies in children have been made with the cyanide method we have examined 11 normal children and found that the circulation time is shorter than in adults, averaging 10.6 seconds (Table I), maximum being 14.5 and minimum 9.0; in one child showing marked excitement and apprehension, a circulation time of seven seconds was

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TABLE I  
CONTROL CHILDREN—ARM-TO-CAROTID SINUS CIRCULATION TIME WITH NACN

| NAME   | AGE | SEX | WEIGHT<br>(LB.)<br>TEMPERATURE<br>(° F.) | AMOUNT OF NACN<br>(2% SOLUTION)<br>INJECTED | CIRCULATION<br>TIME<br>(SECONDS) | PULSE<br>BEFORE | PULSE<br>AFTER | B. P.  | INTENSITY<br>OF<br>REACTION |
|--|-----|-----|--|---|----------------------------------|-----------------|----------------|--------|-----------------------------|
| A. S.  | 10  | F   | 50 lb.<br>T. 98.2                        | 0.17 c.c.-0.15 mg./kg.                      | 9.0                              | 118             | 122            | 85/65  | +                           |
| M. F.  | 10  | M   | 62<br>T. 98.0                            | 0.20 c.c.-0.14 mg./kg.                      | 11.2                             | 110             | 102            | 105/60 | +                           |
| H. D.  | 12  | M   | 85<br>T. 98.4                            | 0.25 c.c.-0.13 mg./kg.                      | 13.5                             | 100             | 85             | 100/70 | +                           |
| C. P.  | 7   | M   | 35<br>T. 99.0                            | 0.16 c.c.-0.18 mg./kg.                      | 10.8                             | 114             | 100            | 90/60  | ++                          |
| A. C.  | 11  | M   | 56<br>T. 98.0                            | 0.17 c.c.-0.13 mg./kg.                      | 11.5                             | 88              | 74             | 95/65  | ++                          |
| N. M.  | 8   | M   | 38<br>T. 98.0                            | 0.15 c.c.-0.17 mg./kg.                      | 10.0                             | 80              | 78             | 105/70 | +                           |
| S. C.  | 10  | M   | 65<br>T. 98.0                            | 0.17 c.c.-0.11 mg./kg.                      | 9.0                              | 120             | 114            | 110/50 | ++                          |
| S. K.  | 7   | F   | 50<br>T. 97.8                            | 0.17 c.c.-0.11 mg./kg.                      | 9.0                              | 78              | 90             | 95/60  | ++                          |
| L. J.  | 12  | F   | 92<br>T. 98.6                            | 0.20 c.c.-0.095 mg./kg.                     | 10.0                             | 108             | 114            | 130/75 | ++                          |
| T. H.  | 12  | F   | 85<br>T. 98.6                            | 0.20 c.c.-0.10 mg./kg.                      | 12.0                             | 108             | 120            | 110/65 | ++                          |
| J. G.*   | 11  | M   | 65<br>T. 98.0                            | 0.17 c.c.-0.11 mg./kg.                      | 7.0                              | 132             | 130            | 130/60 | ++                          |
| <i>Children With Slight Elevation of Temperature</i> |     |     |  |   |                                  |                 |                |        |                             |
| D. W.<br>Rheumatic<br>fever                          | 8   | M   | 49<br>T. 100.5                           | 0.18 c.c.-0.15 mg./kg.                      | 8.0                              | 112             | 114            | 99/50  | ++                          |
| R. J.<br>Rheumatic<br>fever                          | 11  | M   | 59<br>T. 100.5                           | 0.20 c.c.-0.15 mg./kg.                      | 12.0                             | 114             | 120            | 90/50  | +                           |
| G. B.<br>Acute tonsil-<br>litis                      | 10  | M   | 60<br>T. 99.8                            | 0.20 c.c.-0.15 mg./kg.                      | 10.2                             | 114             | 104            | 100/65 | ++                          |

\*This patient was very apprehensive and excited.



TABLE II  
CHILDREN WITH SEPTAL DEFECT (VENTRICULAR) WITHOUT CYANOSIS OR PULMONARY STENOSIS

| NAME  | AGE | SEX | WEIGHT<br>(LB.)<br>TEMPERATURE<br>(° F.) | AMOUNT OF NRCN          | CIRCULATION<br>TIME<br>(SECONDS) | PULSE<br>BEFORE | PULSE<br>AFTER | B. P.  | INTENSITY<br>OF<br>REACTION |
|-------|-----|-----|--|-------------------------|----------------------------------|-----------------|----------------|--------|-----------------------------|
| J. H. | 7   | M   | 40 lb.<br>T. 98.2                        | 0.18 c.c.-0.20 mg./kg.  | 12.0                             | 98              | 100            | 85/50  | +                           |
| C. H. | 11  | M   | 85<br>T. 98.6                            | 0.20 c.c.-0.10 mg./kg.  | 12.5                             | 102             | 98             | 100/65 | +                           |
| G. N. | 16  | M   | 150<br>T. 98.4                           | 0.25 c.c.-0.075 mg./kg. | 13.0                             | 92              | 88             | 110/70 | ++                          |
| M. M. | 6   | M   | 45<br>T. 98.0                            | 0.15 c.c.-0.14 mg./kg.  | 13.0                             | 106             | 114            | 90/50  | ++                          |
| C. M. | 5   | M   | 40<br>T. 98.4                            | 0.15 c.c.-0.16 mg./kg.  | 10.0                             | 114             | 118            | 85/60  | ++                          |

TABLE III  
TETRALOGY OF FALLOT

| NAME  | AGE | SEX | WEIGHT<br>(LB.)<br>TEMPERATURE<br>(° F.) | AMOUNT OF NRCN         | CIRCULATION<br>TIME<br>(SECONDS) | PULSE<br>BEFORE | PULSE<br>AFTER | B. P.  | INTENSITY<br>OF<br>REACTION |
|-------|-----|-----|--|------------------------|----------------------------------|-----------------|----------------|--------|-----------------------------|
| C. R. | 7   | M   | 50 lb.<br>T. 98.0                        | 0.18 c.c.-0.16 mg./kg. | 3.8                              | 112             | 100            | 85/60  | +++                         |
| W. S. | 10  | M   | 65<br>T. 98.4                            | 0.18 c.c.-0.12 mg./kg. | 4.8                              | 98              | 98             | 90/55  | ++                          |
| M. H. | 13  | F   | 85<br>T. 98.0                            | 0.20 c.c.-0.11 mg./kg. | 4.0                              | 86              | 90             | 100/65 | ++                          |

obtained. This shortening of the circulation time in normal children as compared to adults may be due to the excitement incident to the procedure and the accompanying acceleration of the pulse rate. However, the shorter distance from the arm to the carotid artery in children as compared with adults is probably an even more important factor.

Using the same technique we have examined 5 children with congenital heart disease without morbus caeruleus. The circulation time for this group, most of whom were thought to have uncomplicated interventricular septal defects, averaged 12.1 seconds (Table II).

The clinical data regarding the three patients which we believe have patent interventricular septa with right-to-left shunt are summarized in Table III and in the case reports. None of these patients here described have been autopsied. However, the clinical diagnosis of tetralogy of Fallot was concurred in by three clinicians in each case.

#### CASE REPORTS

CASE 1.—M. H., a white female, aged thirteen years, has had constant cyanosis since birth. The patient complained of marked dyspnea on exertion and attacks of dizziness and fainting. There was marked cyanosis of the lips, tongue, conjunctivae, and nail beds, with a dusky flush of the cheeks. There was moderate clubbing of the fingers. The heart on examination revealed slight enlargement to the right and left with a loud systolic murmur heard best in the third left interspace 2 cm. to the left of the sternum. The pulmonic second sound was accentuated. Fluoroscopy verified the slight enlargement and showed prominence of the pulmonary conus and heavy lung fields. There was only moderate pulsation of the conus and no movement of the hilum shadows. Electrocardiogram showed right axis deviation. Red blood cells numbered 6,000,000; whole blood viscosity was 6 (Hess viscosimeter); circulation time was 4.0 seconds—cyanide.

CASE 2.—W. S., a white male, aged ten years. Cyanosis was first noticed at the age of two years, and has been severe and constant since. Dyspnea and dizziness were present on exertion. There were several small hemoptyses. There was marked cyanosis of the nails, lips, tongue, and conjunctivae with marked clubbing of fingers. There was a loud systolic murmur to the left of the sternum in the second interspace; pulmonic second sound was accentuated. Fluoroscopy revealed slight enlargement to the right and left, with normal waistline and blunting of the apex. Electrocardiogram showed marked right axis deviation. Red blood cells numbered 6,200,000; whole blood viscosity was 6.5; circulation time was 4.8 seconds—cyanide.

CASE 3.—C. B., a white male, aged seven years, has had constant cyanosis since birth. Dyspnea has been of moderate degree. Cyanosis of lips, mucous membranes, conjunctivae, and nail beds was marked. The skin had a dusky appearance. Marked clubbing of toes and fingers was present. Heart was enlarged to right and left with loud harsh systolic murmur, loudest at the second left interspace.  $P_2$  was diminished in intensity. Fluoroscopy revealed enlargement of moderate degree to both right and left with decreased radiovisibility of both aortic and pulmonic shadows and diminished pulsations in the region of the pulmonary conus. Electrocardiogram showed marked right axis deviation. Red blood cells numbered 7,000,000; blood viscosity was 7.2; circulation time was 3.8 seconds—cyanide.

We studied two additional patients with morbus caeruleus in whom it was impossible to elicit a reaction with the cyanide even to the point of doubling the calculated dose (one of the patients received 0.5 c.c. without any reaction). It was noticed that the blood viscosity was tremendously elevated in these two cases, being 9.0 and 10.6 respectively. The slowing of the flow consequent to the increased viscosity might afford an opportunity for diffusion and inactivation of the cyanide.

#### DISCUSSION

Examination of the results shows that in the three cases exhibiting clinical evidence of patent septal defects with venous-arterial shunt the circulation time averaged 4.2 seconds, while in the control group the average value was 10.6 seconds. In one child with fever the circulation time was 8.0 seconds and in another who was apprehensive and crying the reaction occurred in 7.0 seconds. The three patients with the tetralogy of Fallot were calm and placid during the examination, and their lack of excitement made the rapid end point even more convincing and clean cut.

It seems clear that patients with increased blood viscosity, normal blood pressures, and normal pulse rates could not possibly have increased the velocity of the flow by 100 per cent. It is also obvious that a "short circuit" via the patent septum would eliminate the necessity of circulation through the lungs. Hence the stimulating drug need only pass directly from the right to the left ventricle and thence to the carotid sinus, shortening the pathway and giving an apparent increase in the velocity of flow.

In simple patency of the interventricular septum without increased right intraventricular pressure, we would not anticipate shortening of the circulation time as right-to-left shunting of the blood would not be expected. Thus only with pulmonary stenosis or other intrapulmonary lesion causing right ventricular hypertrophy and rise in the right intraventricular pressure plus septal defect would one anticipate a shortened circulation time. It seems clear that interauricular septal defects, patency of the foramen ovale, or patent ductus arteriosus would likewise reduce the circulation time if factors favoring a right-to-left shunt were present. We have so far had no opportunity to study such cases.

We have observed the cases with septal defects closely for a second respiratory response several seconds after the initial reaction which might be due to a portion of the cyanide traveling the long road through the lungs. In none of the cases was a second and delayed response noticed. The amount of cyanide passing through the lungs may have been too small to cause carotid sinus stimulation, or diffusion and inactivation of the cyanide may have been a factor in the failure to elicit a second response.

## SUMMARY AND CONCLUSIONS

1. In three cases of congenital heart disease with the clinical diagnosis of venous-arterial shunt, the circulation time averaged 4.2 seconds. This rapid circulation time is probably pathognomonic of right-to-left shunt.

2. The arm-to-carotid sinus circulation time of eleven normal children averaged 10.6 seconds with the sodium cyanide method of Robb and Weiss.

3. In five patients with acyanotic congenital heart disease, most of whom were thought to have uncomplicated interventricular septal defects, the average circulation time was 12.1 seconds.

4. It is recommended that the cyanide test be used as an aid in the diagnosis of a venous-arterial shunt in cases of congenital heart disease.

We are indebted to the pediatric department for affording us the opportunity of studying these cases.

## REFERENCE

1. Robb, G. P., and Weiss, S.: A Method for the Measurement of the Velocity of the Pulmonary and Peripheral Venous Blood Flow in Man, *AM. HEART J.* 8: 650, 1933.

## A NEW APPARATUS FOR RECORDING HEART SOUNDS\*

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FOR the past two years we have been working with devices for the amplifying and recording of heart sounds. Our available equipment consisted of a No. 2 and a No. 3 mobile type Hindle electrocardiograph. After considerable experimenting it was found possible to arrange them so that both light fields could be focussed on one camera, that of the No. 3, and fairly well equalized. Two different leads, or one in duplicate, could be taken (Fig. 3A) and were apparently identical with those taken in the usual manner. A small amount of parallax was present.

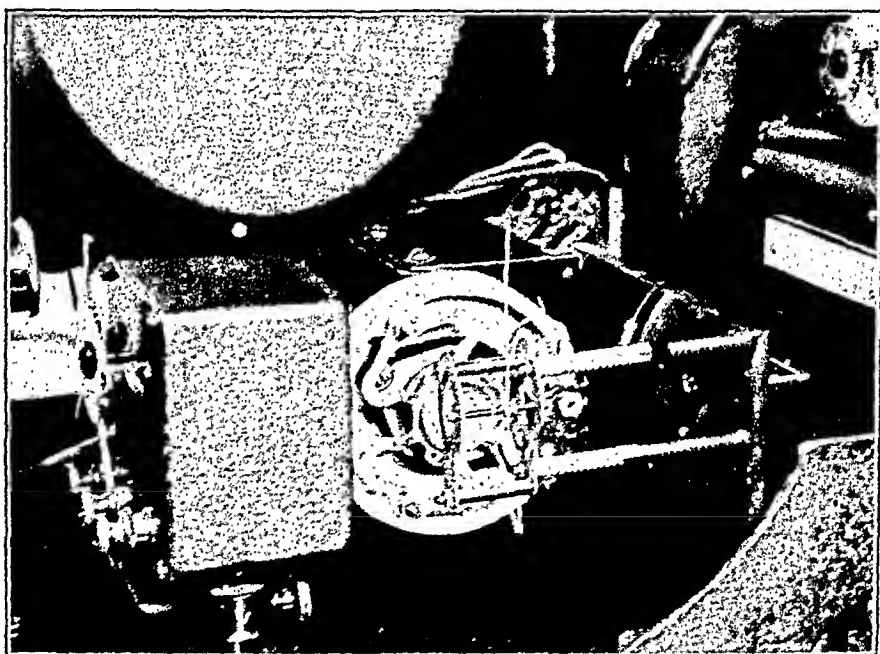


Fig. 1.—The recording unit.

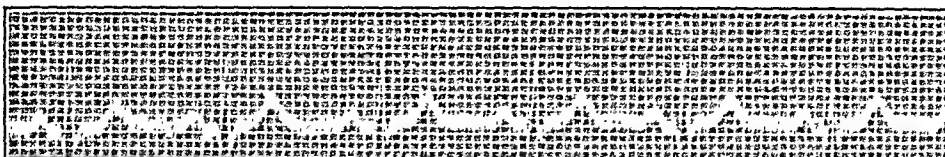
Sound records were made by means of a hook-up, furnished by Mr. A. W. Krause of Northwestern University, and one of the electrocardiographic strings. The tracings obtained by us were not satisfactory and as considerable time was required for the setup the method was abandoned and a simpler one sought. One of us (L. M. S.) conceived the idea of using a radio loud speaker unit, the magnetic type being selected because of its responsiveness and light weight, no cone being used (Figs. 1 and 2). A thin metal rod or needle was attached directly to the moving coil and placed in the light field of one of the electrocardiographs so as to cast a shadow beside that of the string. Good focus was obtained at varying distances from the camera and the unit could be used with either of the machines.

\*Published with the authority of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn.

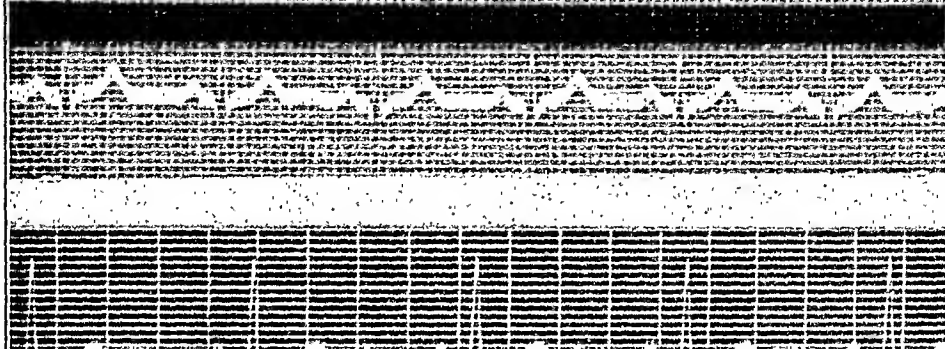


A special attenuator with four fixed steps and a variable control to subdivide them is employed, and the output of this unit is fed into the main circuit through a shielded cord. There are two 6C6 tubes in the main amplifier with the suppressor and screen grid tied to the plate. They are resistance-coupled and feed two 6B5 tubes in push-pull. Shielding is also necessary in the input stages of this amplifier although not so important as in the preamplifier.

A.



B.



C.



Fig. 3A.—Lead II taken simultaneously on No. 3 (upper tracing) and No. 2 (lower tracing) Hindle electrocardiographs. A small amount of parallax is present. The black area was made by the shadow of the shield used to separate the two light fields.

Fig. 3B.—Lead II and heart sounds from the apex of a patient with a normal heart.

Fig. 3C.—Lead II and sound tracing from the apex region of a patient with free aortic insufficiency, positive blood Wassermann reaction and 4 plus Kahn test, negative blood culture and signs suggesting mitral stenosis. A presystolic murmur is shown and was an important lead in establishing this diagnosis. Autopsy showed mitral stenosis and bacterial endocarditis of the aortic valve.

Headphones may be used in either first or second stage and a six-pronged socket is so arranged that one pair of contacts may be used for them, one for a magnetic or dynamic speaker, and the third for the recording apparatus. This

device may be used with any "shadow type" electrocardiograph with regulation bromide paper, the same time-lines serving for both sound and electrocardiographic records. The standard five-spoke or special single-spoke time wheel may be used.

Both Bowles and Ford type stethoscope object pieces have been tried but better tracings were obtained with the microphone itself applied directly to the chest wall. It was found that low frequency murmurs were more easily depicted than the higher pitched ones as has been the experience of other workers. Some attempt was made to cut out the lower frequencies but no satisfactory results were secured from the little work done.

Certain advantages seem apparent in the above apparatus over other devices in use. It is mobile and can be readily attached to or detached from the electro-

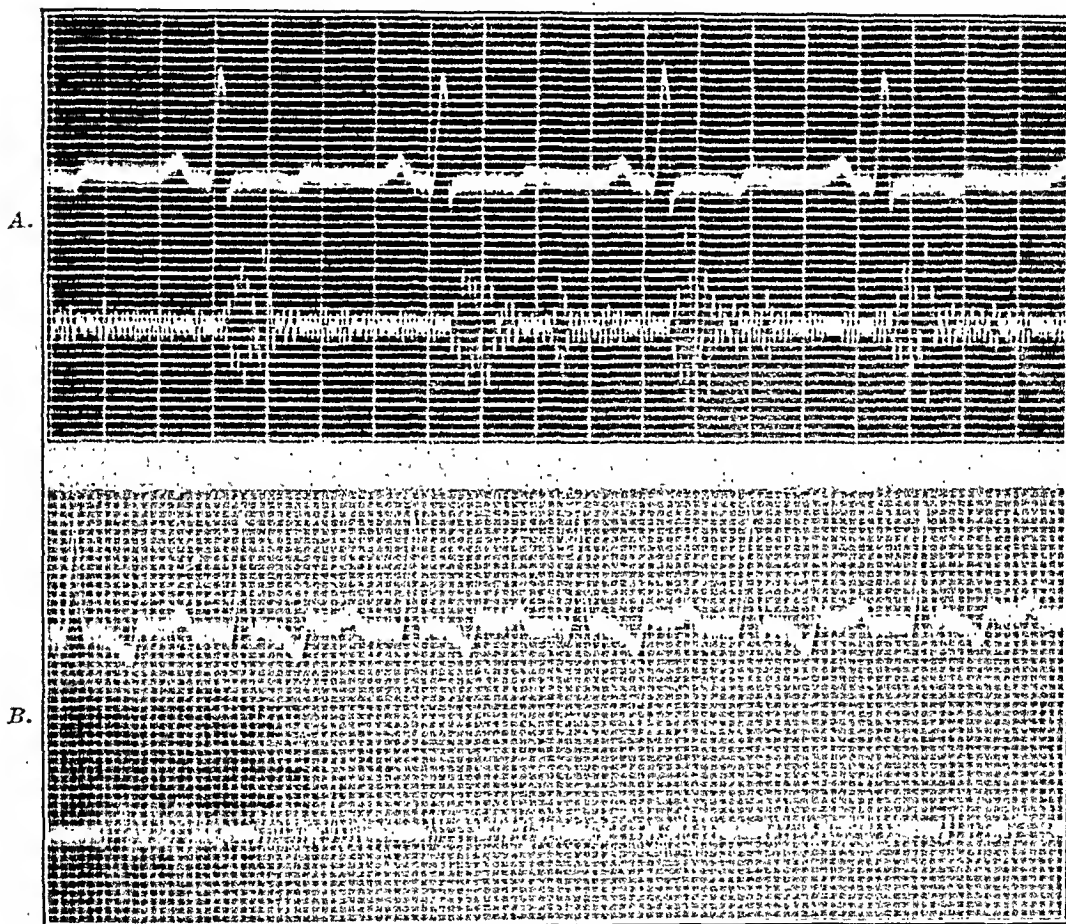


Fig. 4A.—Lead II and sound tracing from the third left interspace. Clinical diagnosis was syphilitic aortitis with well-marked double murmur.

Fig. 4B.—Lead II and sound tracing from second left interspace of a patient with syphilitic aortitis and unusually long diastolic murmur.

cardiograph. Since the sound record is a shadow, it is possible when the electrocardiogram is, and one set of time-lines is used for both.

#### SUMMARY

A new apparatus for recording heart sounds is described, consisting essentially of an amplifier and magnetic radio speaker with a needle casting the shadow comprising the tracing attached directly to the moving coil. Advantages it is believed to possess over similar devices now in use are enumerated.

The authors wish to thank Dr. F. N. Wilson and Dr. Paul F. Barker of Ann Arbor for valuable suggestions.



# Department of Clinical Reports

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## ACQUIRED INTERVENTRICULAR SEPTUM DEFECT

### REPORT OF A CASE

DEAN F. STANLEY, M.D.

DECATUR, ILL.

**A**MONG the rare, but very interesting, complications of coronary thrombosis is an acquired defect in the interventricular septum produced by rupture through an infarct involving that structure. Altogether some twenty cases of the condition have been reported in the literature, of which the case to be reported is, as far as I have been able to find, the third in which the correct diagnosis has been made during life. Although it has been stated that rupture of the septum probably imposes no great additional burden on these hearts which usually are extensively involved by infarction, it was our impression that our patient was greatly shocked by the rupture, and that her clinical course was downhill thereafter.

### CASE REPORT

Mrs. C. E. E., housewife, aged sixty-one years, was first seen in her home at 7:00 A.M. on April 8, 1936, by Dr. A. F. Goodyear. She had been well until the early morning of that day when she was awakened by upper epigastric pain radiating upward and to both arms. This was followed by severe and frequent vomiting. The heart was not enlarged to percussion; the tones were somewhat distant and no murmurs were heard. Temperature was 97.3° F., pulse 60, and the blood pressure was systolic 140, diastolic 86 mm. Morphine sulphate,  $\frac{1}{4}$  grain, was given by subcutaneous injection with some relief of the substernal pain. The pain in the arms persisted for several hours thereafter. At 9:00 P.M. on April 9, 1936, the patient entered Decatur and Macon County Hospital with the diagnosis of suspected coronary thrombosis. Urinalysis at that time showed an amber, acid urine, sp. gr. 1.016, a trace of albumin, and no sugar. There were 10 to 15 pus cells to the high-power field, an occasional red blood cell and an occasional hyaline cast. Blood study showed a hemoglobin of 84 per cent (Sahli); red blood cells, 4,270,000; white blood cells, 9,800. A differential count gave 61 per cent of polymorphonuclears of which 3 per cent were band forms, 33 per cent lymphocytes, 4 per cent monocytes and 2 per cent eosinophiles. Blood sugar was 120 mg.

The patient gradually improved until the evening of April 11, when following the giving of an enema for distention, and while she was on the bedpan, she was stricken with substernal pain and went into shock with sweating, cyanosis, and dyspnea. There developed at this time a loud, harsh, systolic murmur accompanied by a thrill, located in the fourth interspace just to the left of the sternal border. This persisted relatively unchanged until death. A pericardial friction rub was also heard at this time. Blood pressure was systolic 100, diastolic 60 mm. The patient was in a

precarious condition for two weeks following this episode with dyspnea, air hunger, vomiting, and exhaustion. The blood pressure fluctuated between 98/46 and 118/56

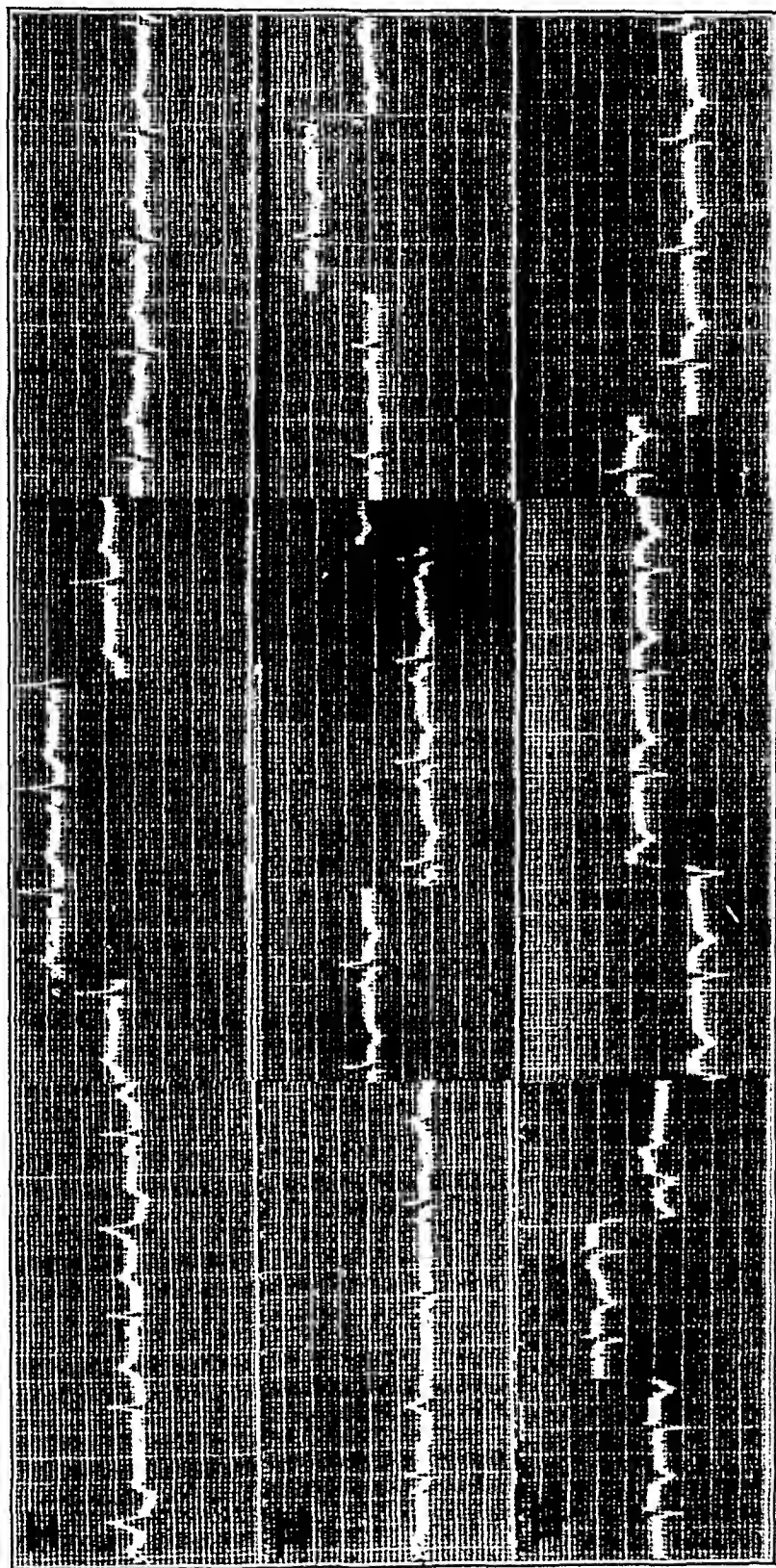


Fig. 1.—Serial electrocardiograms on patient. See text for description. A, tracings made April 24, 1936; B, tracings made May 5, 1936; and C, tracings made June 1, 1936.

during this period. Dr. M. E. Rose saw the patient in consultation on April 12 and was in attendance with Dr. Goodyear for ten weeks thereafter. The patient was first seen by the author on April 24 at which time an electrocardiogram was taken.

This showed low QRS complexes in all leads: cove-plane R-T intervals with a high take-off in Leads II and III; occasional ectopic beats, all from the same focus and apparently ventricular in origin: slight left ventricular predominance. A diagnosis of coronary thrombosis of the  $T_2$  type was made. Other tracings were taken on May 5, 1936, and June 1, 1936, which showed the usual further changes characteristic of serial electrocardiograms taken on patients with acute coronary occlusion. On May 28, 1936, the following note was made on her chart by the author. "I wish to get in writing here my diagnosis of perforation through an infarct in the inter-ventricular septum as a cause for the sudden development on April 11, 1936 of the loud systolic murmur and definite thrill to the left of the ensiform process."

After many vicissitudes with episodes that were interpreted as small infarctions from emboli involving lungs, brain, and kidneys, the patient left the hospital not substantially improved on July 30, 1936. At home she remained in bed under the care of a nurse. She showed evidence of increasing decompensation. Right hemiplegia developed and death occurred on Sept. 14, 1936.

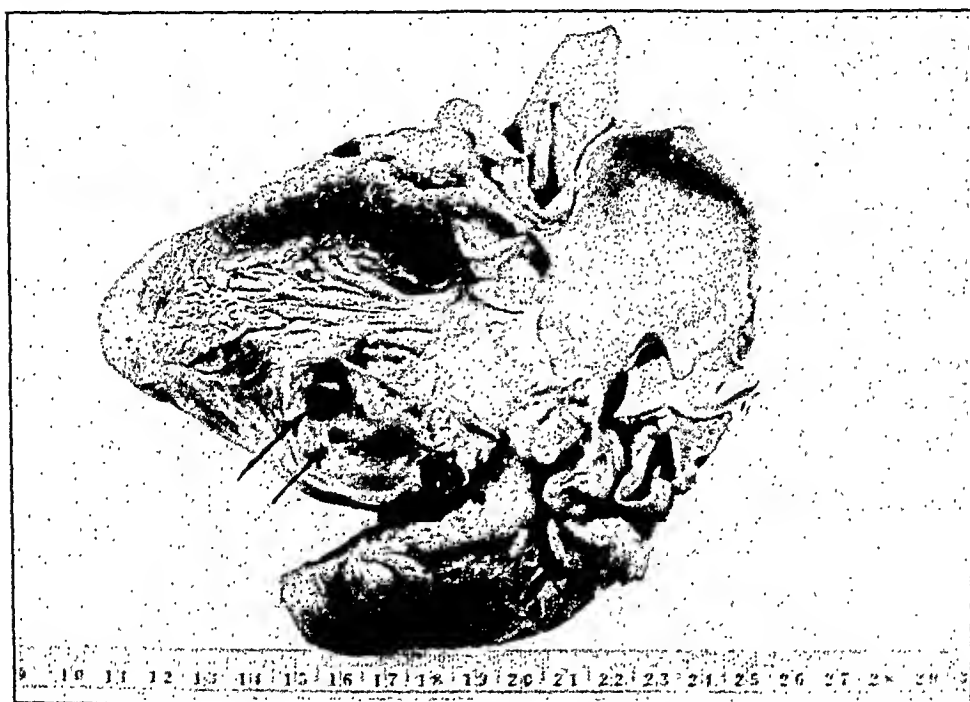


Fig. 2.—Photograph of heart of patient. Arrows point to the two perforations in the interventricular septum.

*Abstract of Autopsy Report.*—Dr. Perry J. Melnick, pathologist.

At autopsy the findings of cardiac decompensation were quite marked, and included pitting edema of the lower extremities, 2,000 c.c. of clear yellow fluid in the abdominal cavity, 100 c.c. of similar fluid in the pericardial sac, 3,500 c.c. and 1,000 c.c. of similar fluid in the right and left pleural cavities, respectively, which compressed both lungs, and passive congestion of the abdominal viscera. The important findings were in the heart. The heart weighed 350 gm. The left ventricle was in general 18 mm. thick, but the posterior wall of the left ventricle was reduced to a thickness of 3 to 4 mm. and was composed of firm whitish tissue—microscopically seen to be scar tissue—which bulged backward, forming an aneurysm. The adjacent one-half of the interventricular septum was similarly composed of a thin layer of firm scar tissue. Near the center of this scarred area in the septum was an oval hole 12 mm. in diameter with smooth edges, and just posterior to this large defect was

a smaller one 3 mm. in diameter. The right and left ventricles communicated through these openings. The remainder of the myocardium was soft and deep chocolate brown. The right ventricle was 8 mm. thick and the conus pulmonalis was very distinct. The valves were all unchanged, and the aorta above the valve was 80 mm. in circumference with only a few fatty and hyaline plaques in the intima.

In the right coronary artery about 2 cm. from the orifice there was a large calcific plaque which completely encircled the lumen and produced an almost complete stenosis. The remainder of the right coronary as well as the left coronary arteries had a moderate number of hyaline and calcific plaques.

Anatomical diagnosis: Ancient myomalacia, with aneurysmal bulging of the posterior part of the left ventricle of the heart, and of the adjacent one-half of the interventricular septum. Multiple (2) spontaneous perforations of the interventricular septum. Severe sclerosis of the proximal portion of the right coronary artery with marked stenosis of the lumen. Bilateral hydrothorax, hydropericardium, ascites, and anasarea. Chronic passive congestion of the lungs, liver, spleen, and gastrointestinal tract. Compression atelectasis of both lower pulmonary lobes. Moderate eccentric hypertrophy of the heart, especially of the right ventricle, with brown atrophy of the myocardium.

Since Sager<sup>1</sup> has reviewed the literature on perforation of the infarcted septum in coronary thrombosis and has very adequately discussed criteria for diagnosis and differential diagnosis, no useful purpose would be served by further discussion here. Since his article appeared, two other cases have been reported, those of Kepler, Berkman, and Barnes,<sup>2</sup> and Gross and Schwartz,<sup>3</sup> in neither of which, however, was the condition diagnosed ante mortem. Brunn and Sager made correct ante-mortem diagnoses in their cases, and the present is therefore, as far as we can determine, the third such case reported.

#### REFERENCES

1. Sager, R. U.: Coronary Thrombosis: Perforation of the Infarcted Interventricular Septum, *Arch. Int. Med.* 53: 140, 1934.
2. Kepler, E. J., Berkman, J. M., and Barnes, A. R.: Acute Myocardial Infarction With Rupture of the Interventricular Septum, Complicated by Hyperglycemia Without Glycosuria: Report of a Case, *Proc. Staff Meet., Mayo Clin.* 10: 209, 1935.
3. Gross, Harry, and Schwartz, Sidney P.: A Case of Acquired Interventricular Septal Defect Associated With Long-Standing Congestive Heart Failure, *AM. HEART J.* 11: 626, 1936.

# Department of Reviews and Abstracts

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## Selected Abstracts

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Radnai, P.: The Action of Acidity on the Heart Muscle. *Ztschr. f. Kreislaufforsch.* 29: 18, 1937.

The author found that therapeutic doses of ammonium chloride had no effect histologically on the heart muscle of the rabbit. Larger doses lead to degeneration and round cell infiltration.

It was found that in 3 out of 17 cases in man abnormalities in the electrocardiogram developed: in 2 an A-V block appeared and in a third an intraventricular block appeared. There is thus a risk of aggravating conduction disturbances with acid salt therapy in large doses.

L. N. K.

de Boer, S., and Brouwer, A.: The Action of Hydroquinine, Hydroquinidine, Quinine P and Quinidine P on Heart Rate and Refractory Phase. *Ztschr. f. Kreislaufforsch.* 29: 52, 1937.

All these drugs cause an increase in heart rate and a prolongation of the refractory phase.

L. N. K.

Scarff, R. W., and McGeorge, Murray: Experimental Renal Lesions and Blood-Pressure in Rabbits. *Brit. J. Exper. Path.* 18: 59, 1937.

Many workers have produced hypertension in experimental animals by means of a direct attack upon the kidneys while others, using the same or similar methods, have been unable to achieve the same results. The authors have studied the effect upon the blood pressure in rabbits of various forms of renal injury, including oxalate nephritis, unilateral and bilateral nephrectomy, trauma, ligation of ureters, and glomeruli embolism of inert material and killed material in previously sensitized animals. The blood pressure determinations were made by means of carotid loops prepared according to the method of van Leersum. The blood pressure of normal rabbits was determined to be a mean of 96 mm. in systolic pressure with a range of 74 to 120 mm. The blood pressure of the rabbits was carefully standardized over a period of at least two weeks before any of the procedures was carried out. In six rabbits, oxalate nephritis was produced by the injection of varying quantities of oxalate crystals intravenously. Unilateral nephrectomy was performed fourteen days prior to the oxalate injections in two of the animals. Simple embolism was produced in a group of rabbits previously subjected to unilateral nephrectomy, by injection of laked red blood corpuscles directly into the renal artery. Seven rabbits survived long enough to make satisfactory blood pressure studies. In one of the rabbits, the remaining kidney was removed, and in another the ureter was ligated. Killed streptococci were injected into the renal arteries of five previously sensitized rabbits.

Although in many of the animals considerable impairment of renal function was caused by these various procedures, in none was there found a significant rise in blood pressure.

E. A. H.

Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities: An Experimental Analysis in Monkeys. *Brit. J. Surg.* 24: 787, 1937.

Sympathectomy for relief of severe vasospastic states of the lower extremities has been successful for many years. However, it was not usually successful in the upper extremities until J. C. White pointed out that the conventional operations severed preganglionic fibers to the foot, whereas in the operation for the hand postganglionic fibers were cut. White showed that the failure of postganglionic section of the sympathetics to the hand was due to sensitization of the muscle of the vessel coat to adrenalin. He and his coworkers have recently published a series of cases of sympathectomies on the upper extremities of patients with vasospastic disorders, performed by preganglionic section. The results have been good—as good as those of the conventional operation in the lower extremities.

The study of the present authors is on the Rhesus monkey, in which the sympathetics have much the same anatomical arrangement as in man. Studies of skin temperature following heating of the body and following injection of adrenalin have been made. On 12 monkeys sympathectomies of the conventional, old type were performed in the upper extremity. In only one of these has a good degree of vasodilatation persisted, and in at least 2 the sympathectomized side was more sensitive to cold than was the normal side. Eleven of the 12 developed an adrenalin sensitivity about 10 times the normal, whereas one was about half as sensitive as the others. When the lumbosacral sympathetic chain was excised (2 animals—postganglionic section of lower extremities), the result was much the same. In 8 monkeys the thoracic chain was cut just above or below the third thoracic ganglion (preganglionic section). In none of these has the sympathectomized side constricted as much as in the case of the postganglionic sections. Adrenalin sensitivity is only about one-third as intense as after postganglionic section. The experimental data agree with the recent conclusions of White and his coworkers on the advisability of the new type of sympathectomy for vasospasm of the upper extremities.

H. M.

Tannenberg, Joseph: The Rôle of Allergy in the Pathogenesis of Progressive Thrombosis, Especially in Regard to Changes in the Endothelial Lining of Large Peripheral Veins. *Arch. Path.* 23: 501, 1937.

The author, in agreement with some and in contradiction to other authors, finds no conclusive evidence in favor of experimental thrombus formation by allergic processes, although he agrees that repeated injections of antigen can injure the vessels.

Twenty-four rabbits were used. Each animal was prepared by nine intravenous injections, over the course of three weeks, of some one antigen. Sheep serum and killed pneumococci and streptococci were used. From seven to eighteen days after the last of these injections the right jugular and femoral veins were made narrower by means of ligatures placed aseptically. The antigen (living or killed) was then injected into another vein and the animals were killed twenty-four hours later. The control animals were of two sorts: those fully prepared but receiving in all one dose of antigen. The jugular and femoral veins of the controls were constricted by ligature. Several sections of various veins were stained and studied. In a high percentage of the immunized rabbits (both those fully treated and the fully immunized controls) small inflammatory lesions were found in the pulmonary arteries and in the heart, and this occurred only once in 50 of those control animals which received a single injection only. This obviously does not imply that these lesions have allergic origin. None progressed to thrombosis.

What thrombi did appear appeared only near the points of constriction by ligature and were no more frequent in immunized than in nonimmunized controls, apparently indicating that the thrombi that appeared were of traumatic origin.

H. M.

Freyberg, R. H.: Relation of Experimental Atherosclerosis to Diets Rich in Vegetable Protein. *Arch. Int. Med.* 59: 660, 1937.

Newburgh and Squier (1920) and Newburgh and Clarkson (1923) have shown previously that a diet rich in animal protein produces atherosclerosis in rabbits. Eight of 11 animals that were fed a diet containing 27 per cent animal protein for more than six months became atherosclerotic. The occurrence and extent of the sclerosis is roughly proportional to the duration of feeding of meat. It had also been shown that the cholesterol content of these diets was too small to be the cause of the atherosclerosis.

The present authors studied the effect on rabbits of feeding diets rich in proteins of vegetable origin. Diets containing 33 and 37.8 per cent of vegetable protein fed to twelve rabbits for as long as eleven months failed to produce atherosclerosis.

H. M.

Grant, F.: Circulation in Pneumothorax. *Deutsches Arch. f. klin. Med.* 178: 670, 1936.

Forty patients in whom pneumothorax was performed for tuberculosis were studied. The pulse was found to be slightly slower following pneumothorax, and there was less sinus arrhythmia. Ventricular extrasystoles were produced in 8 cases. In all instances the electrocardiogram showed a right axis deviation due doubtlessly to a depression of the diaphragm. Occasionally there occurred reversible changes in the S-T and T-waves.

L. N. K.

Nothhaas: The State of the Peripheral Circulation in Health and Disease. *Klin. Wchnschr.* 15: 778, 1936.

The author determined heat elimination of the right hand by a calorimeter. He found that the intracutaneous wheal produced by uolan caused a sharp decrease in heat elimination in the normal man (40 men of from twenty to fifty years of age). In 30 patients with gastric ulcers and 11 with bronchial asthma this stimulus was found to cause an increase in heat elimination in two-thirds of the cases. The other one-third showed a small decrease.

L. N. K.

Jores, A.: The Role of the Hypophysis in High Blood Pressure, Especially in Essential Hypertension. *Klin. Wchnschr.* 15: 841, 1936.

Serum extracts of some patients with high blood pressure in which serum albumin had been precipitated by sulphosalicylic acid caused an increase in adrenal cortex of infantile mice. This resembles the response to corticotropic hormone. The two products resemble each other chemically also. This adrenal-cortex-stimulating substance was found in six cases of essential hypertension. It was not present in any of the eight examined patients with eclampsia and pregnancy toxemias. In four cases of renal high blood pressure and pneumonia, a noticeable cortical response was found in one and a slight one in the other three. It

was present in all six cases of apoplexy occurring in essential hypertension. The author believes that the results indicated that he has demonstrated that the hypophysis does play a rôle in hypertension.

L. N. K.

Raab, W.: Excitability of the Vasomotor Centers in Man. *Klin. Wchnschr.* 15: 851, 1936.

Excitability of vasoconstrictor center increases with age in man when the blood pressure is normal. In acute nephritis the excitability is unchanged; in hypertension and arteriosclerosis it is markedly increased. Hypophysial material has no effect on excitability. Morphine and luminal decrease the excitability of the center in hypertensive patients. Carbon dioxide changes affect the vasomotor centers of old and established hypertensive patients much as anoxemia and local acidosis of the centers do in animals.

L. N. K.

Flaxman, Nathan: Auricular Fibrillation. *J. A. M. A.* 108: 797, 1937.

Auricular fibrillation, the most common form of arrhythmia in hypertensive heart disease, occurred in 158 (25.3 per cent) of 623 patients with this disease. It definitely influenced the course of the disease in forty-four patients (27.8 per cent) in whom the rapid irregularity preceded and precipitated the congestive heart failure and led to an early death from this cause within one month after the onset in eight (18.1 per cent) of the forty-four patients. When the auricular fibrillation occurred after congestive heart failure had been present from one month to several years, it had no apparent influence on the course of the disease except in relation to the cause of death and the comparative absence of additional occurrences common to appear in hypertensive patients.

AUTHOR.

Klisiecki, A., and Flek, S.: The Circulation in the Coronary Arteries of the Heart.

#### I. The Minute Volume Flow. *Ztschr. f. Biol.* 97: 7, 1936.

In dogs weighing 8 to 25 kilograms the flow in the coronary sinus was found to be 100 c.c. per 100 gm. heart per min. on the average. The size of the coronary arteries depends on the aortic pressure, the state of contraction of the heart muscle and the tone of the coronary vessels. Enlargement of the coronary vessels by elevated arterial pressure or decreased tone accompanying anoxemia increases the coronary flow.

#### II. The Movement of Blood in the Coronary Arteries. *Ztschr. f. Biol.* 97: 12, 1936.

The rate of flow in the coronary artery at normal aortic pressure and heart rate is constant. When the arterial pressure is high and the rate slow, the flow is slower during systole than diastole. The contracting heart offers resistance to flow, and, when powerful enough, it stops flow entirely. Yet when contraction is increased following elevation in pressure, the minute volume is increased, the increase in flow during diastole compensating for the decrease during systole. A systolic acceleration of flow (such as described by Höchrein) occurs only when the coronary vessels constrict.

#### III. Movement of Blood in the Coronary Sinus. *Ztschr. f. Biol.* 97: 19, 1936.

Flow in the coronary sinus depends on pressure and the ventricular contraction pressure. Changes in the right auricle have no effect. During ventricular



systole, there is an acceleration of flow. Slowing the heart decreases flow in the coronary sinus as the pressure within it falls during the long pauses. The heart has a massaging action on this flow.

**IV. The Problem of Vasomotor Nerves—Action of Adrenalin.** *Ztschr. f. Biol.* 97: 23, 1936.

There is a proportionality between the increase in aortic pressure and coronary flow. Soon after adrenalin one finds a decrease in flow when aortic pressure does not change and the heart does not accelerate. The so-called coronary dilator action of adrenalin is due to an increase in mechanical factors which accelerate coronary flow.

**V. Action of Vagi, Pilocarpine and Carotid Sinus Reflex on the Coronary Flow.** *Ztschr. f. Biol.* 97: 34, 1936.

The decrease in flow following vagus stimulation is due to a decrease in cardiac contraction and a fall in blood pressure. When arterial pressure is prevented from falling, an increase in coronary flow is found. The coronary vessels appear to be dilated by the vagus. Pilocarpine causes an increase in coronary flow when the heart is at a standstill. The carotid sinus reflex affects the coronary flow secondarily by its effect on the mechanical factors controlling coronary flow.

L. N. K.

**Coburn, Alvin F., and Moore, Lucile V.: The Independence of Chorea and Rheumatic Activity.** *Am. J. M. Sc.* 193: 1, 1937.

One-half of the cases of chorea under observation occurred in nonrheumatic subjects.

Approximately one-fourth of the cases of chorea occurred in quiescent rheumatic subjects.

Approximately one-fourth of the cases of chorea occurred during active rheumatism.

Uncomplicated chorea is accompanied by normal blood sedimentation rates.

Chorea per se does not suffice for the recognition of the rheumatic subject nor for the diagnosis of rheumatic activity.

AUTHOR.

**Gross, Louis, and Friedberg, Charles K.: Lesions of the Cardiac Valves in Rheumatic Fever.** *Am. J. Path.* 12: 855, 1936.

There are described the incidence and gross and microscopic appearances of lesions in the valves, valve pockets, and chordae tendineae occurring in 97 cases of rheumatic fever. These cases are divided into six clinical groups which represent various courses taken by this disease. It is shown that each group presents certain gross and microscopic features which bear a relation to the clinical grouping. Anatomical evidence is presented which suggests that the course taken by the disease as well as the response of the tissue may be determined by the relative state of immunity. This does not, however, imply that rheumatic fever is primarily an allergic disease. New macroscopic and microscopic data are presented on the development of the rheumatic lesions in the valves, and a discussion is given of the factors which determine the spread of infection, the localization of the verrucous and other lesions, the extent of the valvular damage and the pathogenesis of the characteristic deformities of the valvular apparatus. Certain stigmas of the

rheumatic process occurring in completely healed valves are described. These supply additional data which are of value in elucidating the pathogenesis of other cardiac lesions. A description is also given of the changes which take place in nonrheumatic valves during the first eight decades of life.

AUTHOR.

Page, Irvine H., and Heuer, George J.: Treatment of Essential and Malignant Hypertension by Section of Anterior Nerve Roots. *Arch. Int. Med.* 59: 245, 1937.

Evidence of varied nature indicates that, as part of a more generalized vasoconstriction, vessels of the splanchnic area are narrowed in patients suffering from essential or malignant hypertension. Since no contraindications are known for reduction of the arterial pressure in such patients and there is no known medical treatment of more than temporary value, it appears to be justified to attempt to abolish the extrinsic vasomotor control of this area by section of the anterior nerve roots with the hope of reducing the arterial pressure. It has seemed desirable also to learn more of the part played by the nervous system in the genesis of hypertension. To this end seventeen patients have been subjected to the operation of section of the anterior nerve roots.

No attempt was made to select patients in whom in our opinion a favorable outcome might be anticipated. Six patients showed benign involvement of long duration, three of them with moderate vascular changes and three with severe changes. Six were young women with signs and symptoms of the "hypertensive diencephalic syndrome." Five suffered from highly malignant hypertension. The results of operation are therefore not comparable except within the subgroups.

While the ultimate effect of this operation on the natural course of hypertension cannot be foretold, from a study of these patients for periods of from eight to thirty-seven months after operation, the following results may be listed: (a) Three patients in whom the disease was severe but still benign and without advanced vascular change responded well. (b) One of three patients with more advanced involvement of long standing, with marked sclerotic but benign vascular changes, responded favorably. The headaches were relieved in the second and third cases, but the progress of the disease was unchecked. (c) Six young patients exhibiting the "hypertensive diencephalic syndrome" appeared benefited. (d) Three of those suffering from highly malignant hypertension were unaided by the operation, and two appeared to be improved. The favorable responses have been a marked, prolonged lowering of the arterial pressure, the remission of such symptoms as headache, pressure in the head and easy fatigability and marked improvement in the disposition. Other evidence of improvement in some of the patients has been relaxation of the spasm of the arterioles in the retina (eleven cases), absorption of exudate (two cases), disappearance of papilledema (three cases), and secondary glaucoma (one case), slight reduction in the size of the cardiac shadow in the roentgenograms (eight cases), and reversal of the T-wave from the inverted to the upright position in Lead I (two cases). There has been a definite tendency for a slow rise in pressure to occur over a period of two and one-half years in most, but not all, patients. Judgment must therefore be reserved as to the ultimate effects of the operation on the natural history of the disease.

Although marked anatomical change was present in the vessels of some of the patients, this did not prevent a marked fall in the arterial pressure, which persisted long after the patient had recovered from the immediate effects of the operation. This demonstrates that anatomical changes in the vessels do not account for the persistence of hypertension.

Renal efficiency, as measured by the urea clearance and the ability to concentrate urine, was unchanged either by the partial denervation of the kidneys, which resulted from the operation or from the fall in blood pressure.

In those patients exhibiting the "hypertensive diencephalic syndrome," a marked lowering of the blood pressure did not cause it to disappear. If this syndrome is the somatic expression of irritation of vegetative centers in the brain stem and is not abolished by a reduction of the arterial pressure, it is probably not caused by elevation of the arterial pressure.

The operation of laminectomy does not of itself reduce the arterial pressure for more than several weeks. Transverse myelitis at the eleventh thoracic segment reduces it for prolonged periods (one patient was studied for nine months). These observations, with those concerning the effect of section of the anterior spinal nerve roots on the arterial blood pressure, suggest that the nervous system plays some part in the genesis of hypertension.

Although the operation has markedly improved the clinical condition of many of the patients studied for periods up to two and one-half years, its ultimate value in the treatment of hypertension has not been established.

AUTHOR.

Adson, A. W., and Allen, E. V.: *Essential Hypertension: General Considerations and Report of Results of Treatment by Extensive Resection of Sympathetic Nerves and Partial Resection of Both Suprarenal Glands*. Proc. Inter-State Post Grad. Med. A. North America, 181-191, 1936.

Essential hypertension is a serious disease which seems to account for the deaths of about 23 per cent of all patients who are older than fifty years. Medical treatment is far from satisfactory in many instances. The idea that it is dangerous to lower the blood pressure in essential hypertension has been definitely disproved. The elevation of the blood pressure in essential hypertension is produced by an increased resistance to the flow of blood through the peripheral arterioles. The impediment offered to the flow of blood through the peripheral system in essential hypertension results either from functional changes, that is, vasospasm, or from organic changes, or from a combination of both.

Surgical treatment which is an attempt to diminish arteriolar tone in hypertension has been carried out in a group of patients whose hypertension was progressive and not satisfactorily controlled by medical treatment. The operation performed is a bilateral two-stage resection of the splanchnic nerves, the upper lumbar sympathetic chain and partial suprarenalectomy. The results vary from extremely good to extremely poor. If the blood pressure responds poorly preoperatively to rest, intravenous injection of pentothal sodium, administration of sodium amytal or sodium nitrite, the results of operation are invariably poor. If the blood pressure responds satisfactorily preoperatively to the measures noted, the results of operation are usually but not uniformly good. Patients are benefited symptomatically in a higher percentage of the instances than the blood pressure is satisfactorily influenced. When the blood pressure is satisfactorily reduced by operation, symptoms such as headache and pain in the left thorax are almost uniformly relieved, retinitis may disappear, narrowing and apparent sclerosis of the retinal arteries may be greatly minimized, transverse diameter of the heart may decrease, inverted T-waves in the electrocardiogram may become upright, albumin may disappear from the urine, and the renal function may be improved. As a result of the operation mentioned, the sweating function of the lower extremities is lost and the cutaneous temperature in this region is increased. The menstrual cycle and child-bearing function of the female are not disturbed. Sexual functions and ability of the male are not significantly impaired although ejaculation may not occur with orgasm. Orthostatic hypotension and

tachycardia are commonly noted following operation, but these disappear gradually. Although the interval since the operations have been performed is still comparatively short, there is evidence to justify an opinion that extensive subdiaphragmatic sympathectomy has been of value in reducing the blood pressure in essential hypertension.

AUTHOR.

Kramer, David W.: The Use of Acetyl- $\beta$ -Methylcholine Chloride by Iontophoresis in Peripheral Vascular Diseases. *Am. J. M. Sc.* 193: 405, 1937.

Acetyl- $\beta$ -methylcholine chloride (mecholy) is recognized by investigators as the most desirable preparation of the choline group for peripheral vascular disease.

Iontophoresis, or ionization, is the more direct and logical method of administering it in vascular disturbances. It is simple and practical.

In a series of 30 patients observed in the course of over 350 treatments, there were no serious untoward effects. Twenty-two patients (73 per cent) were benefited, 3 were helped only temporarily and were added to the 5 failures, giving a total of 8 (27 per cent).

The best results were obtained in the vasospastic group, 87 per cent responding favorably and excellently in the small phlebitis series; the diabetic cases showed a 65 per cent favorable response and the Buerger disease group 55 per cent.

Symptomatically, mecholy had a decided influence upon fatigue and cramps regardless of the underlying lesions. It did not control the pain so readily, particularly in the diabetic and thromboangiitis groups.

The results of these observations evidently concur with the findings of those who investigated the pharmacological and physiological properties of acetyl- $\beta$ -methylcholine chloride and suggested that it had possibilities in the treatment of peripheral vascular diseases. While it does not cure, mecholy undoubtedly does give relief in many cases by improving and increasing peripheral circulatory function.

AUTHOR.

Moissejew, S.: Dynamics of the Korotkow Sounds During Application of Warmth to Different Regions of the Body. *Ztschr. f. Kreislaufforsch.* 29: 78, 1937.

In many of 97 observations of blood pressure taken by the auscultatory method during application of heat to various portions of the body, it was noticed that the Korotkow sounds grew very weak (32 cases) or disappeared entirely (21 cases) for a short and variable period of time. The source of heat or the site of application, made little difference except that when larger areas, such as the whole back, were exposed to heat, the sounds were more likely to disappear completely. The change in the sounds occurs after approximately fifteen minutes of heating. The source of heat was, in most of the observations, an infra-red lamp, in a few, hot-water bottles, and in others, a current of hot air.

The author attributes the decrease in intensity of sound to increase in degree of contraction of the smooth muscle of the artery walls. This follows to a certain extent the reasoning of Janowsky. He concludes that on warming the body or parts thereof, a histamine-like substance is released, which stimulates the parasympathetic nerve endings and increases the tone of the large arteries. Unfortunately, records of the frequency of the sounds—records which might have given some information as to changes in elastic state or tone—were not taken. The conclusion drawn seems in this light unjustifiable, but recognition of the phenomenon is of considerable importance.

J. M. S.

Chiari, H.: Concerning the Pathology of Peripheral Vessels. *Wien. klin. Wchnschr.* 50: 395, 1937.

The title is misleading in that remarks are confined entirely to the arteriovenous connections known as glomeri and tumors of these. The successive steps in their recognition and description are clearly and concisely reviewed, an equally clear and brief description of the current studies of microscopic anatomy is given, and the theories advanced as to their function are presented. The author then describes the occurrence of glomus tumors (angio-neuro-myoma) of which he has seen thirty-four cases. They usually occur in the fingers or somewhere on the upper extremity (21 instances) and give rise to pain, burning, and local heat. Because of the local elevation of temperature in these tumors which may be considered as pathologically enlarged glomeri, the author believes that the function of the glomus is one of heat regulation, as first suggested by Hoyer, rather than a regulator of blood pressure and cardiac work.

J. M. S.

Allen, E. V.: The Peripheral Arteries in Raynaud's Disease: An Arteriographic Study of Living Subjects. *Proc. Staff Meet. Mayo Clin.* 12: 187, 1937.

The digital arteries of most patients with Raynaud's disease usually are not filled normally in arteriograms. Two common findings in the arteriograms in such cases are absence of filling of the distal parts of digital arteries and diminished caliber of such arteries. Arteriograms of asthenic individuals who do not have Raynaud's disease may reveal the same changes that the arteriograms in most cases of Raynaud's disease do. Some patients with Raynaud's disease, however, have normal arteriograms.

Cervicothoracic sympathetic ganglionectomy for Raynaud's disease may or may not produce normal filling of digital arteries which did not fill normally before operation. Evidence of intrinsic arterial disease manifested by sudden interruption of the lumen was observed in only two digital arteries and is therefore considered a finding of questionable importance. From an arteriographic standpoint, the digital arteries are not significantly diseased in an organic way in Raynaud's disease. If a "local fault" is responsible for Raynaud's disease, it does not appear in arteriograms as an organic one. Nevertheless, arteriography does not exclude such a "local fault" in Raynaud's disease since the arteriograms reveal changes in only the lumina of the arteries.

AUTHOR.

Roesler, Hugo: A Roentgenological Study of the Heart Size in Athletes. *Am. J. Roentgenol.* 36: 849, 1936.

Four cases are reported and it is demonstrated (1) that the heart in healthy athletes may occasionally reach a size which justifies the diagnosis of slight enlargement and (2) that a diminution may take place after cessation of training.

Rautmann's concept of tests of speed and tests of endurance is given in relation to a possible cardiac response. Kirch's anatomical studies on the hearts of athletes are cited and critically analyzed.

AUTHOR.

Sgalitzer, M., and Demel, R.: Differentiation Between Functional and Organic Diseases of the Peripheral Arteries by Roentgen Ray Studies. *Wien. klin. Wchnschr.* 50: 319, 1937.

The differential diagnosis between the several organic diseases of arteries can often be made with considerable accuracy by injecting opaque fluids into arteries.

"Primary arteriosclerosis" begins with a widening of the arterial lumen and eventually exhibits very irregular narrowing. Endarteritis obliterans and Buerger's disease begin with smooth regular narrowing which slowly progresses. The boundaries of the opaque medium are smooth and clear. Embolic closures of arterial lumina give rise to sharp shadows with a border convex proximally where the filling of the lumen ends abruptly. Spasm of the arteries is often recognizable by the concentric narrowing and by the smooth lance-form end of the shadow. The most important means of distinguishing organic from spastic disease arises, however, from the observation that dilatation of the arteries and arterioles takes place almost immediately after the injection of the solutions of organic iodides such as uroselectan. The authors' procedure has, therefore, been to follow the first injection by a second in ten minutes, to take films after each injection and compare the width of the arterial lumina in the two series of photographs. If the diameter of the vessels is different in the two pictures, the amount of widening in the second is a measure of the degree of spasm which existed. The method is said to be especially useful in distinguishing the relative degree of spasm and of organic disease in cases in which the two are combined. In addition, the authors state that therapeutic effects of release of spasm by the iodide solution have been observed to have a beneficial effect for as long as Leriche's operation upon the nerve supply to the arteries.

J. M. S.

Pearson, Gertrude E. G.: A Note on the Calcium Aspirin Therapy of Chorea. *Canad. M. A. J.* 36: 516, 1937.

Calcium and aspirin were used in 23 cases of Sydenham's chorea with marked clinical improvement and a shortening of the average duration of the chorea.

Spinal fluid calcium estimations in 23 cases of chorea showed that there was no minimum figure below which chorea occurred. Variations in the calcium level in the spinal fluid were found ranging from 2.6 to 6.4 mg. per cent during the attack of chorea and after the chorea had subsided still ranging from 2.8 to 6.6.

With calcium and aspirin 17 cases of chorea showed an increase in the calcium of the spinal fluid, with a disappearance of the chorea; 6 cases showed a decrease in the spinal fluid calcium, also with a disappearance of the chorea. Many of the cases showing an increase later showed a decrease to the former level or below it, with no return of the chorea.

Some patients returned to the hospital several months after discharge with a recurrence of chorea, although the level of the spinal fluid calcium remained the same, or was higher than on discharge.

AUTHOR.

Müller, E. A.: The Action of Cardiozol and the Respiration and Metabolism in Pernoxtonnarcosis. *Med. Klin.* 32: 495, 1936.

The author states that cardiozol in the narcotized dog relieves narcosis, increases both respiration and metabolism and improves the state of both the respiratory and cardiac centers.

L. N. K.

## Books Received

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DIGITALISFIBEL FÜR DEN ARZT. By Dr. Ernst Edens (Düsseldorf). Julius Springer, Berlin, 1937. 39 pages. Price, R.M. 1.80.

LA RADIOKYMOGRAPHIE DU COEUR ET DES VAISSEAUX. By Drs. Émile Bordet and H. Fischgold. Masson et Cie., Paris, 1937. 134 pages with 66 illustrations. Price, 30 fr.

MALADIE HYPERTENSIVE ET SYNDROMES D'HYPERTENSION. By Dr. A. Dumas. Masson et Cie., Paris, 1937. 136 pages. Price, 22 fr.

QUELQUES VÉRITÉS PREMIÈRES (OU SOI-DISANT TELLES) EN PATHOLOGIE CARDIO-VASCULAIRE. By Dr. E. Denzelot. Masson et Cie., Paris, 1937. 82 pages. Price, 24 fr.

A PATOLOGIA DA CIRCULAÇÃO CORONÁRIA: PROBLEMA DA ANGINA PECTORIS, INFARTO DO MIOCARDIO, SÍNDROMA DE ADAMS-STOKES. By Prof. Eduardo Coelho. Livraria Bertrand, Lisbon, 1937. 164 pages.

ESTUDIO FUNCIONAL DEL HIGADO AFECTADO POR EL ESTANCAMIENTO SANGUÍNEO EN LAS CARDIOPATIAS. Thesis by Severo R. Amuchástegui. Imprenta de la Universidad Nacional de Córdoba, 1936. 166 pages.

ROENTGENKIMOGRÁFIA CONCÉNTRICA. By Dr. Alberto C. Morelli. Montevideo, 1936. 34 pages and 34 plates.

# The American Heart Journal

VOL. 14

SEPTEMBER, 1937

No. 3

## Original Communications

### TREPOPNEA AS AN ETIOLOGICAL FACTOR IN PAROXYSMAL NOCTURNAL DYSPNEA\*

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IN A recent publication<sup>1</sup> attention was called to the fact that certain cardiac patients are comfortable in one recumbent position and uncomfortable in another.† This is probably due to movement of the heart in the chest under the influence of gravity. Individuals with this syndrome (trepopnea) usually prefer lying on the right side, and dislike lying on the left, but there are many variations. Persons with well-developed trepopnea are forced to abandon one recumbent position for another by intolerable symptoms, chiefly dyspnea, precordial pain, and cough. Our observations led us to suggest that, in some cases, trepopnea might play a part in the etiology of paroxysmal nocturnal dyspnea; that an attack of dyspnea might occur if a patient, while asleep, rolled into an unfavorable recumbent position. The present paper is a report of further evidence upon this question.

CASE 1.—J. D., a man of thirty-five years, had advanced rheumatic heart disease, mitral stenosis and insufficiency, marked cardiac enlargement, auricular fibrillation,

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†Since the publication of the paper on trepopnea, certain other pertinent references have been found.<sup>2</sup> Nélaton's paper<sup>2a</sup> is the earliest we have seen. He states that "some people cannot sleep on the left side, or if they can, their sleep is troubled and they do not get as rested as they do when they sleep in a favorable position." He mentions two earlier papers, by Arbey and by Piorry, to which we have not had access. Traube<sup>2c</sup> discusses the way in which a sick person learns to assume his most comfortable position. He uses the term "pseudo-orthopnoe" to describe the condition of a patient who assumes the upright position because of pain or cough, not because of dyspnea. (Possibly "pseudo-trepopnea" might be used in a similar way.) Von Duseh<sup>2d</sup> refers to a patient whose anginal attacks were precipitated by lying on the left side. Ebstein<sup>2e</sup> gives a very comprehensive review of all the various position preferences which sick individuals have. He has assembled a voluminous bibliography which we have used freely.

The rest<sup>2f to 2p</sup> are concerned mainly with measuring the degree of cardiac mobility, and with the question of whether the "Cor mobile," "bewegliche herz" or "wanderherz" produces symptoms. Determann<sup>2o</sup> reports the case of a patient with mitral stenosis who could not tolerate lying on the left side. He recognizes clearly that, when certain patients with heart disease lie on the left side, they are apt to have more marked distress than patients with mobile hearts without heart disease.



and definite trepopnea (R P L S).<sup>\*</sup> When supine he experienced dyspnea and discomfort in the chest which forced him to turn. He had had attacks of nocturnal dyspnea since 1933. These paroxysms were his chief complaint. They were severe, lasting thirty to forty-five minutes, compelling him to get out of bed and lean forward. He stated that he had never awakened in an attack without finding himself in the supine position, and that he did not recall awakening on his back without being in the midst of a paroxysm. His wife volunteered the information that she had often seen him asleep on his back "panting" heavily. She had found that if she could roll him over on the right side, the "panting" would stop, whether or not she awakened him in so doing. If she did not turn him on his side, he would, before long, have one of his severe "spells."

CASE 2.—M. H., a woman of thirty-four years, had rheumatic heart disease, mitral insufficiency and stenosis, possible pulmonic insufficiency, moderate cardiac enlargement, left bundle-branch conduction defect, and trepopnea of choice† (R P S L). If she lay on the left side, she experienced shortness of breath, a choking sensation under the sternum, a pressing feeling over the heart, and a sense of fatigue. When first seen on March 2, 1936, the patient stated that she could not rest on the left side; if she turned on that side while asleep, she would wake up at once. We asked her to observe her symptoms and report to us later. When she returned she told us that on March 2 she had gone to sleep lying on the left side, despite moderate discomfort. During the night her husband found her asleep on her left side in a severe fit of "choking." He wakened her and helped her to sit up. She felt "smothered," "very tired," and "dizzy." She did not know what was wrong, but thought she was "ready to pass out." After some minutes she recovered. The patient was seen again on March 8, 1937, complaining of increased dyspnea and fatigue of a month's duration. She stated that occasionally during the past year, and three times during the preceding two weeks, her husband had found her lying on her left side, asleep, in the midst of a "choking attack," and had wakened her. She never experienced these attacks in any but the left lateral position. She obtained relief each time by rolling to the right side. Her sensations, on awaking, were a smothering, choking feeling, marked fatigue, and a "funny, sharp little pain" in the lower sternal region. On April 5, 1937, she came in again, with the report that on April 2 her husband had been wakened from sleep by strangling noises coming from her. He found her lying on the left side, in another severe choking fit. He awakened her, and helped her into a sitting position. She had marked dyspnea and cough for ten minutes, and was drenched with perspiration. After the attack subsided, she lay down on the right side and went to sleep, but even the next morning she did not feel quite like herself. The husband had never found her asleep on her left side, except when she was having an attack. For several days prior to this recent paroxysm of nocturnal dyspnea, she had been exerting herself more than usual helping a woman "clean house."

CASE 3.—R. M., a woman of forty-four years, had hypertensive cardiovascular disease and moderate enlargement of the heart, and suffered with both dyspnea and angina of effort. When we saw her on Nov. 12, 1936, she had trepopnea of necessity (R P S L). If she lay on the left side, she felt a pressing at the apex, extending to the left chest posteriorly (not anginal) and "got all stuffed up and couldn't breathe." She stated that often in the middle of the night, she had wakened lying on the left side, with a "funny, short cough," "all choked up."

<sup>\*</sup>For the sake of brevity, an individual's relative preference for various recumbent positions will be indicated by a series of letters: R—right lateral; L—left lateral; P—prone; and S—supine. The first letter in the series is the most favorable position, the last letter is the most unfavorable. "R P L S" indicates that the patient is most comfortable on the right, least comfortable supine, and has an intermediate preference for the other two positions.

<sup>†</sup>"Trepopnea of choice" and "trepopnea of necessity" are used in this paper in the same sense that "orthopnea of choice" and "orthopnea of necessity" have been used in the past.

When symptoms were mild, she was able to terminate them by turning on her right side. When they were severe, she had to sit up for about five minutes before she could get her breath. She died of cerebral hemorrhage on Dec. 8, 1936. Necropsy disclosed a heart weighing 430 grams, with a thick left ventricular wall and sclerosed coronary arteries.

CASE 4.—G. H., a man of forty-three years, had rheumatic heart disease, moderate cardiac enlargement, mitral stenosis and insufficiency, and auricular fibrillation. Trepopnea (R P S L) was first noted in 1934, during an upper respiratory infection. Since that time it had fluctuated in intensity with variations in his circulatory efficiency. If he lay on the left side he experienced a "blowing up" in his left chest, shoulders, and arms, and felt choked. Sometimes a coughing spell occurred. When his trepopnea was marked, he frequently woke up on his left side in the middle of the night in an attack of dyspnea and cough, and had to sit up for many minutes to get his breath. He was convinced that these paroxysms were produced by turning on the left side during sleep. For some time he had tried to prevent this occurrence by putting a pillow close to his back as he lay on the right side so that he would have to "roll up hill" to get on the left side.

CASE 5.—M. C., a man of forty-two years, had syphilitic aortic insufficiency, marked cardiac enlargement, and congestion of the lungs. Trepopnea (P L R S) first appeared with the onset of congestive failure in January, 1936. The symptoms induced by lying on his back were dyspnea, choking, and discomfort in the center of the chest. In January, 1936, he began having the experience of waking up in the middle of the night, feeling short of breath and tired, as though he "had been running." He stated that he was usually lying on his back at such times. On further questioning he was not absolutely certain of this, but stated that the attacks must have been caused by lying on his back, because the sensations with which he awoke were identical with those he experienced during the day when he lay on his back for any length of time. On June 13, 1936, he entered the hospital with engorgement of the veins and liver, with no pulmonary congestion. Trepopnea and paroxysmal nocturnal dyspnea had both disappeared, but he preferred sitting to lying. He died of lobar pneumonia on Oct. 2, 1936. The heart weighed 900 grams and showed syphilitic aortic insufficiency.

CASE 6.—N. M., a woman of forty-three years, had congestive heart failure, syphilitic aortic insufficiency, large uterine fibroids, and a combination of trepopnea with orthopnea (R P S L). On Jan. 21, 1936, she was asked to lie on her left side. Within a minute she was forced to sit up, coughing and breathing heavily. The attack lasted five minutes. She stated that she often had attacks of this sort at night, which awakened her from sleep, but that when she awoke she was on her back, as a rule, not her left side. She died on March 7, 1936. The heart weighed 550 grams and showed syphilitic aortic insufficiency.

CASE 7.—W. S., a boy of seventeen years, had congestive heart failure, rheumatic mitral and aortic valvular disease, marked cardiac enlargement, and trepopnea of necessity (R S P L). When on the left side, he became cyanosed, the respiratory rate increased and he complained of pain in the right upper quadrant and a sense of choking. He stated that he had never experienced nocturnal dyspnea because he never had lain on the left side, even during sleep. On the night of March 17, 1937, the patient was asleep, lying on the right side. One of us turned him on the left side without waking him. He stayed in that position for twenty seconds. Then, without waking, he returned to the right lateral position. A second time he was turned on the left side. After fifteen seconds, he turned on the right, still asleep. A third time he was turned on the left side. This time he stayed there for a minute.

He then became quite dyspneic, woke up, sat bolt upright, almost before he was completely awake, breathed hard for half a minute, lay down on his back and went to sleep. The next morning, he had no recollection of these events. From March 17 to March 30, 1937, observation by the ward nurse demonstrated the fact that he never slept on his left side. On the latter date we again turned him into that position while he was asleep. He lay there for about half a minute. Then he began to cough and to breathe more forcefully. Shortly thereafter he awoke, and sat up coughing and breathing heavily for five minutes. After the cough subsided and breathing became normal, he lay down on his back and went to sleep. This paroxysm was like the one of March 17 except that it was of longer duration, cough was a prominent feature, and he remembered the episode the next morning. During the first week of April congestive failure began to subside. At the same time trepopnea diminished markedly. At a later date (April 24, 1937) the patient was able to sleep on his left side in apparent comfort.

The evidence supplied by the foregoing case reports would seem to warrant the following statements: (1) The manifestations of paroxysmal nocturnal dyspnea closely resemble certain of the symptoms of trepopnea: they seem identical to an observer, and to some patients who have experienced both. (2) Certain individuals with trepopnea, who have paroxysmal nocturnal dyspnea, believe that their nocturnal attacks are caused by the involuntary assumption of an unfavorable recumbent position during sleep. This belief is based upon their finding themselves in an unfavorable recumbent position whenever they awake in a paroxysm, and upon their being able to terminate mild attacks by turning over. The belief is so firmly fixed in some, that it has led them to adopt preventive measures (Case 4). (3) The wife in Case 1, and the husband in Case 2, felt convinced that the paroxysms of nocturnal dyspnea of their respective partners were produced by the assumption of one recumbent position, and were prevented or aborted by the assumption of another. (4) One man (Case 7) awoke with a paroxysm of nocturnal dyspnea when he was turned on the left side during sleep.

*Consequently, it would seem that in some individuals, trepopnea is an etiological factor in paroxysmal nocturnal dyspnea.*

These are selected cases, however, which illustrate only one aspect of the problem. Trepopnea and paroxysmal nocturnal dyspnea are not always associated in such an obvious etiological relationship.

(1) *There are patients with paroxysmal nocturnal dyspnea who do not have definitely demonstrable trepopnea.*—We have studied four such individuals. Two said that their attacks occurred only when they lay on the left side (Cases 8 and 9). Two others stated that they had no set position in which they awakened in attacks. (Cases 10 and 11.)

(2) *There are patients with paroxysmal nocturnal dyspnea and trepopnea who do not recognize an etiological relationship between the assumption of their unfavorable recumbent position and their nocturnal attacks.*—One patient had no knowledge of awakening with his attacks

in any constant position (Case 12). One believed that her position on awakening was not always an unfavorable one (Case 13). Three were convinced that their positions on awakening were often favorable ones (Cases 14, 15, and 16). It is true that individuals do not always know what they do at night (Case 7). Some of these patients may not really know in what position they awake. Moreover, they may produce their attacks by lying in their unfavorable position and may turn to a favorable one just before waking. Nevertheless, one should give as much attention to their negative testimony as to the positive statements of Cases 3 to 6, until one has the opportunity of testing their accuracy by watching them at night.

(3) *There are many patients with trepopnea who do not have attacks of nocturnal dyspnea.*—When this fact first came to light, it seemed difficult to understand. Most people are said to change position frequently during sleep. Therefore, it seemed reasonable to expect a trepopneic patient to get into his unfavorable recumbent position at some time during the night, and to be awakened by the ensuing symptoms. Study of the problem has shown that this is exactly what does occur. Most patients with trepopnea do awake at night with discomfort, which they believe to be caused by lying in an unfavorable position. However, dyspnea may be mild or absent. They may complain of (a) pain, anginal (Case 17), nonanginal (Cases 18, 19, 20, 21, and 22); (b) a combination of pain and dyspnea (Cases 23, 24, and 25); (c) palpitation (Case 26); (d) cough (Case 27); (e) indefinite sensations, probably a combination of dyspnea, palpitation, and discomfort (Cases 28, 29, and 30); (f) bad dreams (Case 31). Many of these symptoms have been mentioned by Weiss and Robb<sup>3</sup> as “equivalent manifestations of mild cardiac asthma.”

There are a few patients with trepopnea who do not awake at night with the symptoms of this syndrome. First, there are individuals with mild degrees of trepopnea who can sleep in their most unfavorable recumbent position<sup>1</sup> (Cases 15 and 16). Second, there are persons who seem to be able to avoid their unfavorable position subconsciously without waking. One of our patients (Case 32) could probably do this; another (Case 7) certainly could.

Finally, it should be mentioned that there are persons with two unfavorable recumbent positions whose statements suggest that they avoid the worse subconsciously and awaken with cardiac symptoms in the better of the two (Cases 6 and 19).

(4) It has been reported that nocturnal dyspnea is common in aortic disease and hypertension, whereas it is uncommon in mitral stenosis and auricular fibrillation.<sup>3, 5</sup> This has not been found true of trepopnea. It is our impression that cases of these different types are wak-

ened with equal frequency by cardiac symptoms, but that patients with mitral stenosis and auricular fibrillation are less likely to have dyspnea as their primary symptom, and are more prone to experience palpitation and precordial discomfort; if attacks of dyspnea occur, they are apt to be of brief duration. The statement is also probably justified that dyspnea, as the primary cardiac awakening symptom, is less likely to be found in the patient with extreme congestive failure and severe trepopnea, than in the individual with cardiac insufficiency of lesser degree. It seems that a patient must be able to endure sleeping in his most unfavorable position for a considerable period, in order to bring on a severe, prolonged paroxysm of dyspnea. This does not appear to be possible for the most markedly trepopneic individuals.

The writings of Weiss and Robb,<sup>3</sup> Harrison,<sup>4</sup> and White and his co-workers<sup>5</sup> have included practically all available knowledge concerning the etiology of paroxysmal nocturnal dyspnea. It is probably the general impression that this knowledge is incomplete: that, in most instances, an adequate exciting cause for the attack has not been evident. Consequently, on the basis of the additional evidence contained in this paper, it might be worth while to review the subject.

It would appear that practically all cases of paroxysmal nocturnal dyspnea have a *predisposing factor*—something which produces an actual or latent failure of proper blood flow from the lungs to the aorta. This may be (a) left ventricular failure, (b) mitral valve obstruction, or (c) any other condition which might interfere with egress of blood from the lungs. In addition to this, a *precipitating factor* seems to be necessary—anything which can produce a sudden intensification of this failure of proper blood flow from the lungs to the aorta. This may be (a) the assumption of an unfavorable recumbent position during sleep (orthopnea or trepopnea), (b) a dream which gives rise to emotional disturbance or to physical effort, or in occasional cases<sup>6</sup> the onset of a paroxysm of arrhythmia or of a coronary occlusion. Conditions which may exaggerate the predisposing factor from time to time or facilitate the operation of a precipitating factor are hot weather,<sup>4</sup> abdominal distention<sup>4</sup> (stomach, bowels, or bladder), respiratory infection, and undue physical or emotional activity during the day. Furthermore, a low serum protein or an allergic tendency may increase the respiratory distress of an attack by superimposing upon it pulmonary edema and bronchospasm.

The recognition of trepopnea as a precipitating factor<sup>6</sup> supplies an explanation for the onset of attacks in many instances, which in the

<sup>6</sup>That others have been interested in a similar line of thought is shown by the following: Harrison,<sup>4</sup> in discussing the causes of paroxysmal nocturnal dyspnea, mentions the position of the body as an important factor. After describing the effect of orthopnea he states "some persons are likely to be short of breath when lying on the back, and some when lying on the left side." Weiss and Robb<sup>3</sup> recorded the fact that change from the supine to the prone position resulted in cessation of an attack, and that bending the head forward exerted a favorable effect.

past have appeared to have no adequate cause. Perhaps this concept will fill the most important gap in our knowledge of the etiology of paroxysmal nocturnal dyspnea.

If it can be demonstrated that an individual is likely to have an attack of paroxysmal dyspnea when he assumes a certain recumbent position during sleep, an attempt should be made to prevent him from doing so. One method is to fit him with a fairly snug woolen undershirt, with large wooden spools sewed to those sides which the patient should avoid.

Two other points concerning trepopnea might be mentioned: 1. Determann<sup>2-0</sup> made the observation in eight noncardiac patients that, immediately post partum, cardiac mobility increased tremendously. He described a patient whose apex impulse moved 1.5 cm. to the left before delivery. Shortly after delivery, the apex moved 9 cm. to the left, when the patient lay on the left side. The impulse was found, only after prolonged search, high in the axilla. He stated that this increased mobility lasted for several days; longer in multiparas than in primiparas. If his observations are accurate, trepopnea may be a factor in post-partum death in patients with heart disease. We have not as yet had the opportunity of studying this possibility. However, it seems to us suggestive that acute fatal cardiac failure tends to occur some hours after delivery when the patient is resting, rather than during delivery when the patient is subject to physical strain.

2. In our former paper<sup>1</sup> the statement was made that "it might be well, in nursing a cardiac patient, especially if he is narcotized or unconscious, for any reason, to be cognizant of the existence of this phenomenon" (i.e., trepopnea). "The order to turn the patient from side to side every hour may have to be modified." Case 33 demonstrates that this statement was justified. The patient had been trepopneic for some time but had been able to avoid lying on the left side until a cerebral embolus rendered her partly paralyzed and semistuporous. After that the order "turn the patient from side to side each hour" resulted in three serious circulatory attacks. When the etiological relationship of trepopnea to these attacks was recognized, the patient was kept off her left side and had no more such seizures. One of the standard textbooks on internal medicine, in discussing the treatment of hemiplegia, states that "owing to the frequency with which hypostatic pneumonia develops, the patient should be kept off his back and on the paralyzed side as much as possible." In certain patients with trepopnea, an alarming effect may be produced if this recommendation is carried out.

#### SUMMARY

Trepopnea is an etiological factor in the production of paroxysmal nocturnal dyspnea. In certain patients the relationship is definite. In others, however, the two syndromes are not obviously related.

Many persons with trepopnea do not experience paroxysms of nocturnal dyspnea. Some are awakened, when they assume an unfavorable recumbent position during sleep, by symptoms other than dyspnea: especially pain, palpitation, and cough. Some are able to avoid their unfavorable recumbent positions subconsciously, without waking. If a trepopneic individual becomes unconscious or paralyzed, the responsibility for avoiding an unfavorable position may devolve upon the physician and nurse.

Patients with mild degrees of trepopnea usually are capable of sleeping in their most unfavorable recumbent positions. However, if further impairment of blood flow from the lungs to the aorta occurs, either temporary or permanent, the assumption of an unfavorable position during sleep may initiate a severe attack.

The demonstration that trepopnea is a precipitating factor in paroxysmal nocturnal dyspnea supplies an explanation for the onset of attacks in certain cases where formerly no adequate cause was recognized.

#### CASE REPORTS

CASE 8.—On Nov. 16, 1935 a physician (D. T.), fifty-two years of age, consulted us. On three different occasions during the preceding three months he had awakened from a sound sleep with dyspnea so urgent that it had forced him to sit up. Each time he had awakened he had found himself lying on the left side. He volunteered this information without knowledge of our interest in trepopnea. Careful examination of his cardiovascular system elicited no evidence of disease. (This patient was mentioned in a previous paper.)<sup>1</sup>

CASE 9.—Z. W. was seen in the cardiac clinic on March 12, 1936. He was a short, heavy-set negro laborer of forty-five years, with diabetes, a negative Wassermann reaction, dyspnea on climbing stairs, and no definite objective evidence of cardiovascular disease. The tentative diagnosis was coronary artery disease. Trepopnea was not clearly demonstrable. All recumbent positions could be tolerated, but in certain of them symptoms were experienced: The right lateral position made him feel as if his breath did not "go all the way down"; the prone position caused him to be "tired around the heart"; in the left lateral position he felt a "heaviness over the heart," and "every now and then my breath gets a little short"; the supine position was comfortable, if he used two pillows. For a year he had noticed that if he went to sleep on his left side, he would wake up "seared, fightin', and hollerin'." He would think he was in a whirlwind, in a storm, or in the water drowning and trying to escape. When he awoke his heart thumped so hard that he often asked his wife if she could hear it (which she could not). He was badly "choked up" and so short of breath that he had to sit up for three to five minutes. Almost all of these attacks arose when he was on the left side, asleep. He experienced them very occasionally if he lay on his back with his head too low. Both he and his wife stoutly maintained that the "witch-ridin' spells" never occurred in any other recumbent position. These attacks constituted his chief complaint. (This patient was mentioned in a previous paper.)<sup>1</sup>

CASE 10.—A. F. was a forty-one-year-old Italian tailor with extreme hypertension (210/150), slight cardiac enlargement, and slight edema of the feet, who was seen

in the cardiac clinic on Oct. 26, 1936. He had experienced four attacks of nocturnal dyspnea during the preceding two weeks. All but the last had been severe. For years he had slept on his right side by preference. Sometimes he slept on the left side. He said he "no can catch sleep" when he lay on his back, but trepopnea could not be demonstrated. He did not recall awakening in any particular recumbent position when he had his attacks.

CASE 11.—J. S., a forty-nine-year-old Italian man, had degenerative cardiovascular disease and moderate cardiac enlargement. Although he was more comfortable on the right side and back than on the left, trepopnea could not be demonstrated. He had paroxysms of nocturnal dyspnea, which did not seem to him to be related to any particular recumbent position. There was a question of a possible allergic factor, since the attacks were relieved by epinephrine.

CASE 12.—A. H., a colored truck driver, thirty-six years old, had mitral stenosis, auricular fibrillation, marked cardiac enlargement, and trepopnea of necessity (R P S L). Smothering and a sense of fatigue became intolerable if he lay on the left side. About a dozen times during 1936 and the spring of 1937, he had awakened at night "all smothered," without cough, feeling that there "was not enough air in the room," and that he could not get his breath. (He made a motion suggesting that there was a bag covering his head.) At such times he would sit up, get no relief; then get up, "stir around," and go nearer the window. It took about half an hour for the attack to pass off. He did not remember in what position he awoke. However, he said that the sensation with which he awoke was exactly like that caused by lying on the left side, only "much worse."

CASE 13.—L. A., a woman of twenty-nine years, had mitral insufficiency and stenosis, possible pulmonic insufficiency, marked cardiac enlargement and trepopnea of choice (R S P L). On Oct. 6, 1936, she awakened in the middle of the night, lying on the left side, with shortness of breath, and a "short, funny, cough." She rolled to her right side and obtained relief in a few minutes. During the next week, she experienced several similar nocturnal attacks. When questioned on October 12 she stated that almost always when she awoke in an attack she was on her left side. Once or twice she thought she was lying on her back.

CASE 14.—G. C., a man of fifty-seven years, had hypertensive cardiovascular disease, syphilis, slight aortic insufficiency, considerable cardiac enlargement, and trepopnea of necessity (R P S L). He was watched at night by the ward nurse, and was never seen sleeping on the left side. There was a definite history of paroxysmal nocturnal dyspnea, but no attacks were observed while he was in the hospital. He did not believe that he awoke on the left side in attacks, but rather on the right. We attempted to turn him on his left side while he slept, but never succeeded in doing so without awakening him.

CASE 15.—J. R., a forty-eight-year-old Italian man, had hypertensive cardiovascular disease, marked cardiac enlargement, left bundle-branch block, and trepopnea of choice (R P S L). He often awoke with nocturnal dyspnea, but believed that he was in the right supine position (a position which he liked) at such times, not on the left. He said that if he rolled on the left side during sleep, he would wake up with a start, and would have to sit up for a while to get his heart quieted down. However, the ward nurse reported that he often slept on the left side.

CASE 16.—I. P., a man of fifty-one years, had marked cardiac enlargement and congestive heart failure, probably due to coronary artery disease. He had trepopnea of choice (R S P L). He stated that he had often awakened at night in a paroxysm of



dyspnea, but did not believe he had been lying on the left side at such times. The ward nurses reported that he often slept on the left side at night. He was never observed in an attack of nocturnal dyspnea.

CASE 17.—M. G., a colored woman of sixty-seven years, had hypertension, angina pectoris, and moderate cardiac enlargement. She preferred to lie prone or on her right side. If she turned on her back during sleep, or if she slipped down off her two pillows, she would awaken with severe upper sternal pain exactly like that which she experienced on effort.

CASE 18.—J. G., a colored man of fifty-one years, had hypertension, marked cardiac enlargement, and trepopnea of necessity (R P S L). He often woke up at night when he rolled on the left side. The sensation which would waken him was a severe pain over the precordium. It was usually relieved when he turned on the right side. Sometimes it did not disappear until he sat up. The pain was accompanied by a slight choking feeling, but not by real shortness of breath.

CASE 19.—E. W., a woman of twenty-two years, had rheumatic heart disease, mitral insufficiency and stenosis, moderate enlargement of the heart and trepopnea of necessity (P R S L). For a long time she had been wakened about once each night by sharp pain through her left chest, throbbing of the heart, and a moderate sense of choking. At such times she found herself on her back. She could roll over on her face and obtain relief in about five minutes. She had never awakened lying on the left side.

CASE 20.—C. C. was a very large Italian woman, 5 feet in height, who weighed over 300 pounds. She had hypertension, nephritis, moderate cardiac enlargement, and trepopnea of necessity (R P S L). She stated that once every week or two she would wake up at night lying on the left side with a severe pain over her heart, and a marked feeling of fatigue. These symptoms were of such degree that she was powerless to turn by herself. She had to wake her husband, who rolled her on her right side. She then obtained relief. Shortness of breath was not present during these episodes.

CASE 21.—V. R., a man of forty-four years, had rheumatic heart disease, mitral insufficiency and stenosis, auricular fibrillation, marked cardiac enlargement, and trepopnea of necessity (P R S L). He said that once in a long while he rolled on the left side during sleep. Whenever this happened he would wake with pain in the precordium, in the left shoulder, and in the right hypochondrium. Shortness of breath was not a definite feature.

CASE 22.—A. V., a man of fifty-nine years, had rheumatic heart disease, moderate cardiac enlargement, mitral stenosis, auricular fibrillation, and trepopnea of necessity (R P S L). The first three positions were all comfortable. The left lateral position caused precordial pain. He often awoke at night lying on the left side, with a severe "bruised feeling" over his heart. He turned to the right and it disappeared.

CASE 23.—H. B., a man of twenty-four years, had rheumatic heart disease, mitral and aortic valvular lesions, extreme cardiac enlargement, auricular fibrillation, and trepopnea of necessity (L P R S). He stated that he was frequently awakened in the middle of the night, lying on his back or on his right side, by "feeling a heavy weight" on his chest. He was usually a little dyspneic at such times, and might have a brief coughing spell, but as a rule shortness of breath and cough were not the outstanding symptoms.

CASE 24.—L. F., a woman of forty-eight years, had advanced rheumatic heart disease, marked cardiac enlargement, mitral insufficiency and stenosis, auricular fibrillation, and trepopnea of necessity (R S P L). She told us that she often awoke at night, lying on the left side, with pain over her heart, a peculiar heavy feeling in the whole left side of the chest, marked fatigue, and a sense of choking. Dyspnea was secondary, cough was absent. She sat up for a few minutes, then lay down on the right side and went to sleep.

CASE 25.—E. M., a woman of fifty-nine years, had hypertension, severe angina of effort, marked cardiac enlargement, and trepopnea of choice (L R P S). She often awoke at night with a choking sensation, found herself on her back, rolled to one side or the other, and experienced relief. She stated that this sense of choking was a combination of "pressure and smothering."

CASE 26.—M. R. was a colored woman of fifty-five years, who had syphilis, hypertension, moderate cardiac enlargement, and trepopnea of choice (R S P L). She told us, "If I turns on my lef' at night, I wakes right up. I has a scary feelin', and my heart is goin' hard or goin' wrong or somethin'." She also described a pressure over her heart. She did not experience real dyspnea or pain.

CASE 27.—J. F., a man of fifty-five years, had coronary artery disease, angina of effort, and slight cardiac enlargement. Lying on the left side made him cough. He stated that he often rolled on the left side while asleep, but whenever he did, he awoke promptly. He would sit up, belch twice, cough a few times, then lie down on his right side and go to sleep again. Long before we first saw him he made a study of his trepopnea. On several occasions he lay on the left side as long as he could. Coughing spells lasting a minute or two resulted, but he never had a real paroxysm of dyspnea. He believed that the cough saved him from having a bad spell at night, because it wakened him before he got in bad condition. The sensation that caused him to cough was a tickling in the pharynx, not down in the chest.

CASE 28.—C. C., a woman of seventy-five years, had degenerative heart disease, moderate cardiac enlargement, auricular fibrillation, and trepopnea of necessity (R S P L). She had been tested repeatedly, and could never tolerate lying on the left side for much more than a minute. Usually she was forced to change her position in less than thirty seconds. The symptoms she described were a pain over the heart, and a choking, breathless feeling. She stated that she could never sleep on the left side. If she rolled on that side during sleep, she "woke up right away." She did not know what the sensations were which woke her.

CASE 29.—J. P. was a man of thirty-five years who was in the hospital in November, 1935, with congestive failure. He had rheumatic heart disease, mitral and aortic valvulitis, marked cardiac enlargement, and auricular fibrillation. When first admitted he had trepopnea of necessity (R P L S). If he lay on his back he experienced a smothering sensation and cough. He stated that if he turned on his back during sleep he would "wake up right away." He did not know what wakened him. The ward nurse watched him at night and never saw him lying on his back asleep until congestive failure cleared up, and trepopnea markedly diminished.

CASE 30.—R. O. was a woman of twenty-five years, who died in the hospital on Dec. 6, 1935, with congestive heart failure. She had rheumatic heart disease, mitral and aortic valvulitis, marked cardiac enlargement, auricular fibrillation, and trepopnea of necessity (R P S L). During waking hours she could not tolerate lying on the left side for more than half a minute because of shortness of breath, a "stuffy

feeling," and precordial oppression. She said that now and then she awakened at night with a peculiar feeling that "something was wrong," found that she was on the left side, rolled to the right, and became comfortable at once.

CASE 31.—J. H., a colored man of fifty-nine years, had degenerative heart disease and trepopnea of choice (R S P L). He stated that whenever he turned on the left side at night he had awful dreams—that he was running or falling—which woke him up.

CASE 32.—W. A. was a man of twenty-six years who had congenital heart disease, and a rough systolic murmur and thrill at the base of the heart and along the midsternum. There was no cyanosis. The heart was slightly enlarged. Exercise tolerance was definitely reduced. Trepopnea of choice became trepopnea of necessity (P L R S) when he had a cold. He stated that he never got on his back when asleep. He never had found himself in that position on awakening. Moreover, he never had been awakened at night by dyspnea or by throbbing in the chest (the symptoms he experienced during waking hours if he lay supine).

CASE 33.—Mrs. W. W. A. was a patient of fifty-nine years, whose case had been reported to us by a fellow physician. She had rheumatic heart disease, mitral stenosis, auricular fibrillation, and marked enlargement of the heart. On Feb. 23, 1937, she suffered a left hemiplegia, presumably from a cerebral embolus, and became semi-stuporous. In an attempt to prevent hypostatic pneumonia, the nurses were ordered to turn the patient periodically from side to side.

On February 24 her physician received a telephone call to come at once, the patient was having a severe "heart attack." She was reported to be lying on the left side. The order was given to turn her on her back and give her caffeine. By the time the physician arrived, she looked as well as before. This happened twice more, each time when the patient had been turned on the left side. The attacks were alarming. The pulse rose to 140, and became weak. Cyanosis became quite marked. The nurse believed the patient to be dying. After the third attack, she was studied from the standpoint of trepopnea: When turned slightly to the left, she was comfortable. When turned halfway to the left, after ten minutes she became cyanosed, the heart rate increased markedly, the pulse became weak, and the patient "looked terrible," as though she were going to die. Cough was not present. No change was noted in the breathing. Shortly after she was turned off her left side, these alarming phenomena disappeared. When the nurses were asked if the patient ever had had attacks of this sort when not on the left side, they disagreed.

No history of paroxysmal nocturnal dyspnea could be obtained. Prior to the present illness, the patient had told her housekeeper that she did not like to lie on the left side because it made her feel dizzy and light-headed. Needless to say, she has been kept off her left side since the relation between trepopnea and her attacks was discovered.

One other fact came out in discussing the case with her physician: on a certain day, one of the patient's two physicians saw her, thought she was looking very well and gave a cheerful prognosis. Just as he left he asked the nurse to turn the patient on the left side. He felt that, in this position, she would be able to breathe more freely with her right (unparalyzed) side.<sup>6</sup> Ten minutes later, the other physician called, and thought that the patient was moribund.

#### REFERENCES

1. Wood, F. C., and Wolferth, C. G.: The Tolerance of Certain Cardiac Patients for Various Recumbent Positions (Trepopnea), *Am. J. M. Sc.* 193: 354, 1937.

2. a. Nélaton, A.: *De L'Influence de la position dans les maladies Chirurgicales*, Paris, 1851, p. 5.
- b. Hamernik, J.: *Das Herz und Seine Bewegung*, Prag., 1858.
- c. Traube, L.: *Die symptome des Krankheiten des Respirations und Circulations apparats*, Berlin, 1867, p. 2.
- d. Von Dusch, T.: *Lehrbuch der Herzkrankheiten*, Leipzig, 1868, p. 334.
- e. Ebstein, E.: *Ueber Lage und Lagerung von Kranken in diagnostischen und Therapeutischer Beziehung*, *Ergebn. d. inn. Med. u. Kinderh.* 8: 379, 1912.
- f. Ebstein, E.: *Bemerkungen zur klinik der Herzbeuteldefekte*, München. med. Wehnschr. part 1: p. 522, 1910.
- g. Mozer, F.: *Ueber die Beweglichkeit des Herzens bei Lageveränderungen des Körpers*, Inaug. Dissert. Marburg, June 1, 1904.
- h. Rumpf: *Zur Aetiologie und Symptomatologie des hochgradig beweglichen Herzens*, *Deutsche med. Wehnschr.* 29: 41, 1903.
- i. Silbergleit, H.: *Beitrag zur Kenntniss der Herzbeweglichkeit*, *Deutsche med. Wehnschr.* 29: 870, 1903.
- j. Hoffmann, A.: *Acute Herzdilatation und Cor Mobile*, *Deutsche med. Wehnschr.* 26: 306, 1900.
- k. Krehl, L.: *Diseases of the Myocardium*. *Nothnagel's Encyclopedia of Practical Medicine*, American edition, Volume on Diseases of the Heart, p. 429, 1908.
- l. Leusser: *Ueber Wanderherz*, München. med. Wehnschr. 49: 1095, 1902.
- m. Braun, L.: *Das Bewegliche Herz*, Wien. med. Presse 42: 1082, 1901.
- n. Braun, L.: *Ueber das Wanderherz*, *Centralbl. f. innere Med.* 23: 873, 1902.
- o. Determann, H.: *Die Beweglichkeit des Herzens bei Lageveränderungen des Körpers (Cardioptose)*, *Ztschr. f. klin. Med.* 40: 24, 1900.
- p. Determann, H.: *Ueber die Beweglichkeit des Herzens bei Lageveränderungen des Körpers*, *Deutsche med. Wehnschr.* 26: 242, 1900.
3. Weiss, S., and Robb, G. P.: *Cardiac Asthma (Paroxysmal Cardiac Dyspnea) and the Syndrome of Left Ventricular Failure*, *J. A. M. A.* 100: 1841, 1933.
4. Harrison, T. R.: *Failure of the Circulation*, Baltimore, 1935, Williams & Wilkins Company.
5. a. Palmer, R. S., and White, P. D.: *The Clinical Significance of Cardiac Asthma. Review of Two Hundred and Fifty Cases*, *J. A. M. A.* 92: 431, 1929.
- b. White, P. D.: *Weakness and Failure of the Left Ventricle Without Failure of the Right Ventricle*. *Clinical Recognition*, *J. A. M. A.* 100: 993, 1933.
- c. McGinn, S., and White, P. D.: *A Follow-Up Report on the Clinical Study of Two Hundred and Fifty Cases of Cardiac Asthma and a Survey of an Additional Group of Twenty-Two New Cases*, *New England J. Med.* 207: 1069, 1932.
- d. McGinn, S., and White, P. D.: *Acute Pulmonary Congestion and Cardiac Asthma in Patients With Mitral Stenosis*, *AM. HEART J.* 9: 697, 1934.
6. Musser, J. H.: *Internal Medicine*, Philadelphia, 1934, Lea & Febiger, p. 1193.

# CLINICAL STUDY OF A PREPARATION OF SQUILL (URGININ) IN THE TREATMENT OF MYOCARDIAL INSUFFICIENCY\*

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## HISTORICAL NOTE

**S**QUILL is one of the oldest of medical remedies. Prepared from the bulb of the sea onion (*scilla maritima*), it is said to have been introduced into practice by Epiminides or Pythagoras. The earliest reference to it is found in a medical prescription contained in the Ebers papyrus, about 1500 B.C. In Egypt, the plant was worshipped as a protector against evil, and temples are said to have been erected in its honor. Its consumption is mentioned by Galen, particularly as an aid to longevity. Hippocrates used it externally as an irritant; by others it was employed to promote perspiration and the flow of urine. Later, the external application was abandoned, although it continued in high favor as a diuretic, expectorant, and emetic. In a sixth century manuscript of Dioscorides appears an excellent drawing of the squill plant. Gradually, it fell into disuse, apparently because of its tendency to induce nausea and vomiting.<sup>1, 2, 3</sup>

In the middle of the eighteenth century (1746), van Swieten,<sup>4</sup> pupil of Boerhaave, rediscovered and stressed the efficacy of dried, powdered squill in the treatment of dropsy. The effects on the heart largely escaped notice although Francis Home,<sup>5</sup> Professor of Materia Medica in the University of Edinburgh, in 1780 advised large doses and noted that after a few days "nausea and vomiting came on" and the pulse was then "remarkably slow," sometimes 40. In 1784, the eminent Dr. Samuel Johnson was taking "vinegar of squills" with excellent effect, voiding as much as 20 pints in the course of a day.<sup>6</sup> Yet, when in the following year, Withering<sup>7</sup> published his monograph on the foxglove, the sea onion appears to have been largely forgotten and, for over a century and a half, digitalis has maintained, undisputed, its title as the sovereign remedy in the treatment of cardiac disorders.

The position of squill as a member of the digitalis group was recognized by Fagge and Stevenson<sup>8</sup> in 1865, on the basis of its action of the frog's heart, which they observed was similar to that of the foxglove. Dixon and Haynes<sup>9</sup> first prepared a tincture assayed on frogs,

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This investigation was aided by a grant from the Calco Chemical Co., Inc., Bound Brook, N. J.

Read at the Meeting of the American Heart Association, Atlantic City, N. J., June 8, 1937.

in 1906. But it remained for Mendel,<sup>10</sup> in 1918, to describe in detail pharmacological and clinical studies which aroused renewed interest in the drug and indicated its usefulness in cases of cardiac insufficiency. Added impetus was afforded by the work of Stoll<sup>11</sup> and his collaborators, who, in a series of researches extending from 1921 to 1935, isolated and established the chemical formula of the glucoside, scillaren. In 1934, methods were developed for extracting in pure form the two water-insoluble glucosides, scillonin A and B, which are contained in the preparation used in the present study.<sup>12</sup>

#### LITERATURE

The number of publications dealing with the clinical use and experimental study of squill is enormous. Many of the observations on patients are not pertinent to the present discussion because they are concerned with its action in noneardiac disorders. Its effectiveness in the cure of dropsy, due to its diuretic action, was known for centuries; but, as was at first the case with digitalis, no proper distinction was made between the accumulation of fluid in the tissues resulting from cardiac failure and edema developing from other causes. Later, when it was recognized that squill was primarily a cardiac remedy, belonging to the digitalis series with respect to its action on the heart, more accurate clinical observations were recorded. But the effects were variable and inconstant, largely because preparations were used having different content, potency, and absorbability. In 1922, Robinson<sup>13</sup> wrote: "squills, as well as most of the purer derivatives of digitalis, are so poorly absorbed from the gastrointestinal tract that they should never be used for oral administration." Sollmann,<sup>14</sup> in the 1936 edition of his *Manual of Pharmacology*, states that "the poor absorption renders it undesirable as a digitalis substitute."

During recent years, many attempts have been made to isolate various active principles, but most of those obtained have been only a little purer than the crude extracts. A number have been mixtures of several glucosides. Scillaren, previously mentioned, is said by Stoll<sup>11</sup> to have a "high therapeutic index" and to be rapidly eliminated. Numerous reports of its effects in patients have been made.

Thus far, two papers have been published concerning the clinical use of urginin. Carr and Mayer<sup>15</sup> made observations on 85 patients with cardiac decompensation. They concluded that this preparation (then known as scillonin), will produce the usual effects of digitalis. Cardiac irregularities are likely to be the first sign of dangerous intoxication. Nausea does occur and may precede the appearance of arrhythmias; it appears to signify a more advanced grade of intoxication than when due to digitalis. Slowing of cardiac rate to 60 or below is frequent. All of these effects call for temporary cessation of

therapy. A dose of from 8.0 to 12.0 mg., depending on the weight of the patient, may be given within four days to patients who have not taken a drug of the digitalis group within two weeks. The maintenance dose is approximately 0.5 mg. per day, but it may be as low as 0.33 mg. The use of urginin is of advantage in certain persons who take digitalis with difficulty because of gastric distress early in the course of medication.

A study of the effects of urginin on the electrocardiogram was reported by Maher and Sittler.<sup>16</sup> Twenty-five cases of heart disease, with edema, were studied in the Cook County Infirmary. The dosage ranged from 1.0 to 3.0 mg. daily, for varying periods. There was a wide variation in the degree of effect produced, implying either differences in absorption or in the response of the patient. In therapeutic doses, they observed, as with digitalis, changes in the R-T or S-T segments, slight prolongation of the P-R interval and occasional extrasystoles. The ventricular rate was decreased in 21 of 25 patients; the decrease occurred in the presence of sinus rhythm as well as in auricular fibrillation. The effects of over-dosage were the production of frequent extrasystoles, marked prolongation of the P-R interval and auricular fibrillation.

#### MATERIAL AND PROCEDURE

A clinical study was made of the effects of the preparation of squill, known under the trade name of urginin, on 62 patients in the wards of the hospital. Forty-three suffered from congestive heart failure; the cardiac disease was of varied etiology—rheumatic, syphilitic, arteriosclerotic, and hypertensive. The group of 19 without failure, similarly studied for comparison, comprised patients with affections of the heart as well as some ill of other disorders. A standard routine was followed and all observations were recorded graphically on individual charts. Patients were selected for study who had received no digitalis for at least fourteen days. Sedatives were given as indicated. Cascara and mineral oil were used as cathartics.

A control period of three days of rest in bed preceded administration of urginin, except in a few cases in which therapy seemed urgent. The diet was low in salt and bulk. The symptoms and signs of cardiac insufficiency, temperature, heart rate, and fluid intake and output, were noted daily. The patients were also weighed each day, if their condition was satisfactory. Observations of arterial blood pressure, venous pressure, circulation time, vital capacity, leucocyte count, and erythrocyte sedimentation rate were made at frequent intervals. Electrocardiograms were taken daily during the first ten days, and from two to five times weekly thereafter.

## THE DRUG

Urginin\* is derived from *Urginea maritima* and is a mixture, in approximately equal proportions, of 2 of the active, water-insoluble glucosides—crystalline scillonin A and amorphous scillonin B. The process for extracting these glucosides of squill was perfected by Dyas and Ingersoll.<sup>12</sup> Their chemical behavior is still imperfectly understood, so that biologic assay is necessary to insure uniform potency. For clinical use, urginin is put up in tablets containing 0.5 mg. of the mixed glucosides.

Biologic assay by the intravenous cat method has shown that 1 tablet (0.5 mg.) has an average potency of 2.13 cat units.<sup>17</sup> One cat unit contains approximately 0.202 mg.<sup>18</sup> The tablets are said to retain this potency unimpaired for at least one year.<sup>15</sup> In dogs, crystalline scillonin is less than half as cumulative as ouabain and less than one-third as cumulative as digitalis. The acute toxic effects of scillonin in the dog and cat (continuous intravenous infusion) are as great as those of ouabain. In the frog, they are less.<sup>19</sup> When the crystalline and amorphous scillonins are combined, as in urginin, these individual effects are probably modified.

## EFFECTS IN PATIENTS

In the presence of cardiac insufficiency, the results were similar to those customarily obtained with digitalis.<sup>15</sup> The signs and symptoms of congestive failure tended to disappear. As a rule, edema, when present, was lost and diuresis occurred (Figs. 1 to 5). Occasionally, elimination of fluid was not complete and the administration of a mercurial diuretic (salyrgan or mercupurin) resulted in further augmentation of urinary output and continued loss of weight (Fig. 2). In cases of auricular fibrillation, the ventricular rate was slowed (Figs. 1, 2, 3 and 6). As is the case with digitalis, equally striking results were obtained in the presence of regular (sinus) rhythm (Figs. 4 and 5). When improvement occurred, the venous pressure fell, circulation time decreased and vital capacity increased. There was no specific effect on systolic or diastolic blood pressure. Such changes as occurred were apparently associated with alterations in the state of the heart and circulation; they could not be ascribed to the action of the drug.

In the presence of sinus rhythm, the rate was slowed at least 10 beats in about one-half the cases. The effect on rate cannot be ascribed directly to the action of the drug; the heart slows as the circulation improves, and particularly as diuresis occurs and venous pressure falls. In 22 of 24 cases of auricular fibrillation, the ventrien-

\*Urginin is the trade name for a product marketed by the Calco Chemical Co., Inc. It was accepted, in 1934, by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in *New and Nonofficial Remedies*. See J. A. M. A. 103: 1708, 1934.



UNIT NO. 459019  
J.T.-FEMALE  
AGE-51 YEARS

**RHEUMATIC HEART DISEASE (INACTIVE)**  
**MITRAL STENOSIS and INSUFFICIENCY**  
**CARDIAC HYPERTROPHY      AURICULAR FIBRILLATION**

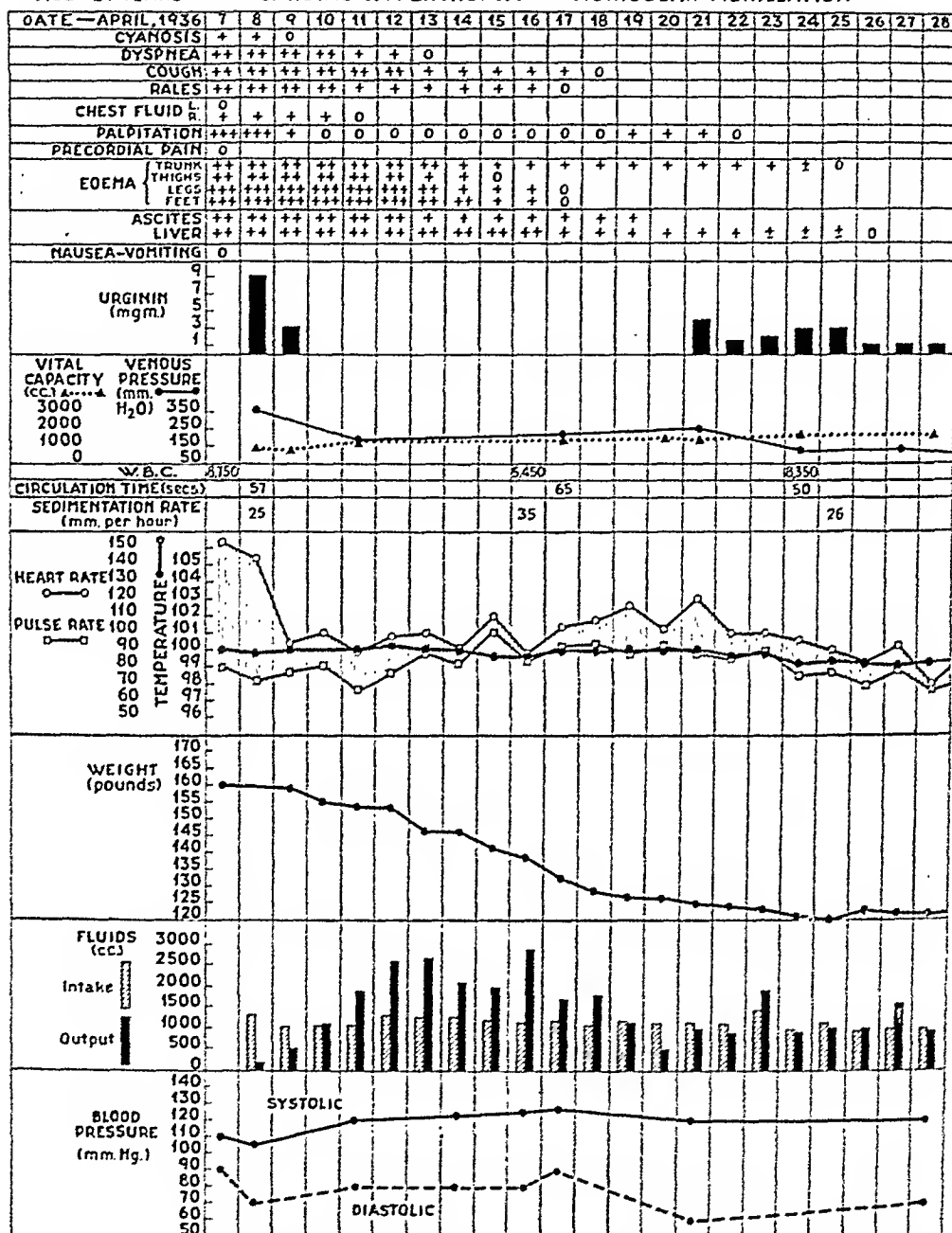


Fig. 1.—Advanced cardiac insufficiency in which the critical condition of the patient made prompt treatment imperative. Administration of 12.0 mg. of urginin in two days was followed by partial relief of symptoms, fall in venous pressure, increase in vital capacity, slowing of heart rate, progressive loss of weight, and marked diuresis. There was no significant change in arterial blood pressure. There were no toxic effects. After stopping urginin therapy, the heart rate became progressively more rapid beginning on the sixth day. The venous pressure rose and the urinary output diminished. Additional doses of urginin, smaller than those originally given, produced greater relief of symptoms and signs of cardiac insufficiency, with further fall in venous pressure and renewed diuresis.



UNIT NO. 475409  
C.C.—FEMALE  
AGE—56 YEARS

**RHEUMATIC HEART DISEASE (INACTIVE)**  
MITRAL STENOSIS and INSUFFICIENCY  
CARDIAC HYPERTROPHY      AURICULAR FIBRILLATION

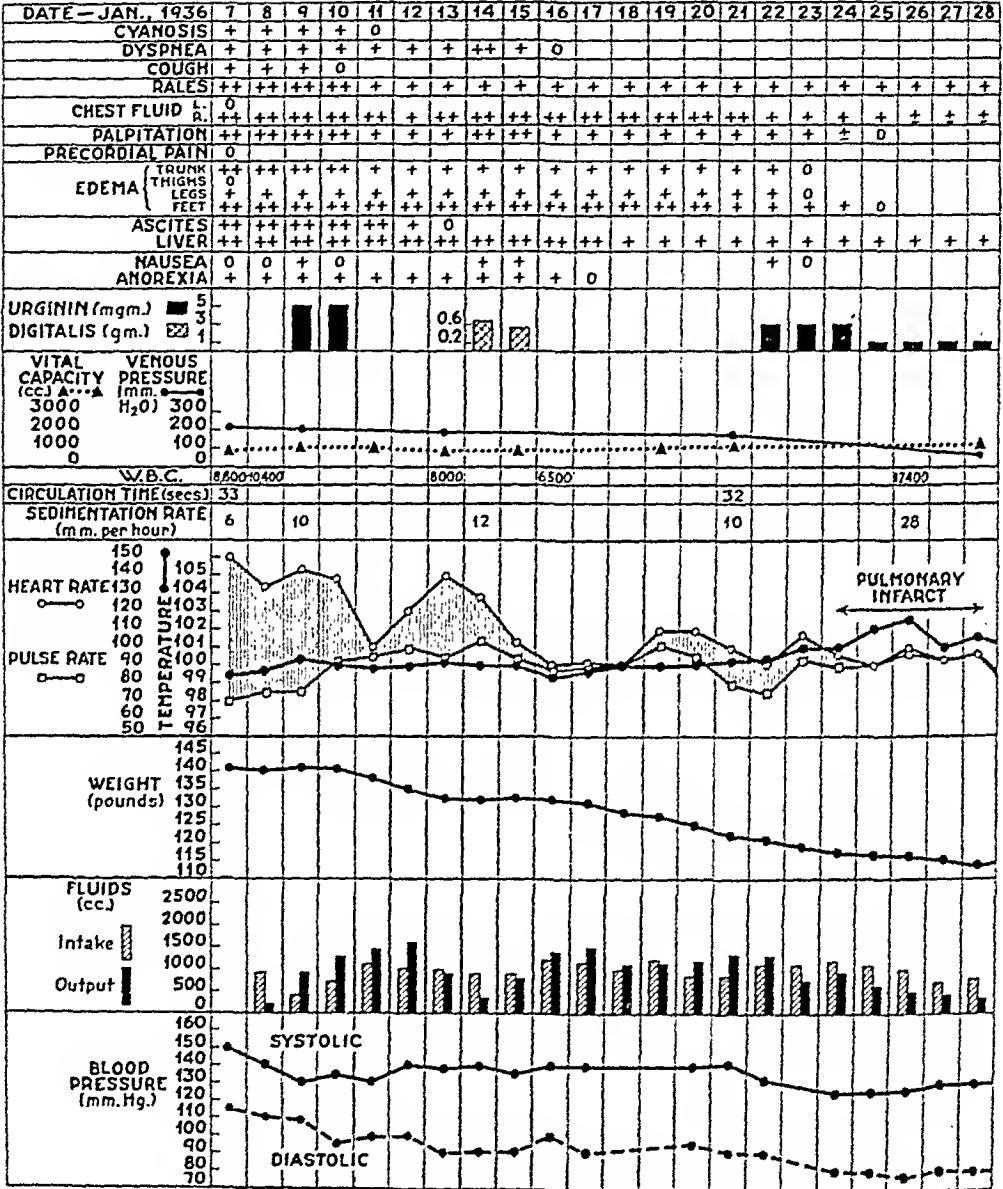


Fig. 3.—(See also Fig. 6.) Advanced cardiac insufficiency with auricular fibrillation and rapid ventricular rate. The heart rate fell from 160 to 100 after 10.0 mg. of urginin, given in two days. There was good diuresis and gradual loss of weight. Urganin was discontinued and after three days, the rate again rose to 140; diuresis and loss of weight ceased. Digitalis, 1.1 gm. of powdered leaf, given in two days, again slowed the rate and induced diuresis with an associated loss of weight. There was further improvement when urginin administration was resumed after an interval of seven days. Pulmonary infarction did not materially interrupt the otherwise favorable course of progress.

UNIT NO. 479422  
G.B. - MALE  
AGE - 63 YEARS

**CORONARY ARTERIOSCLEROSIS  
CARDIAC HYPERTROPHY**

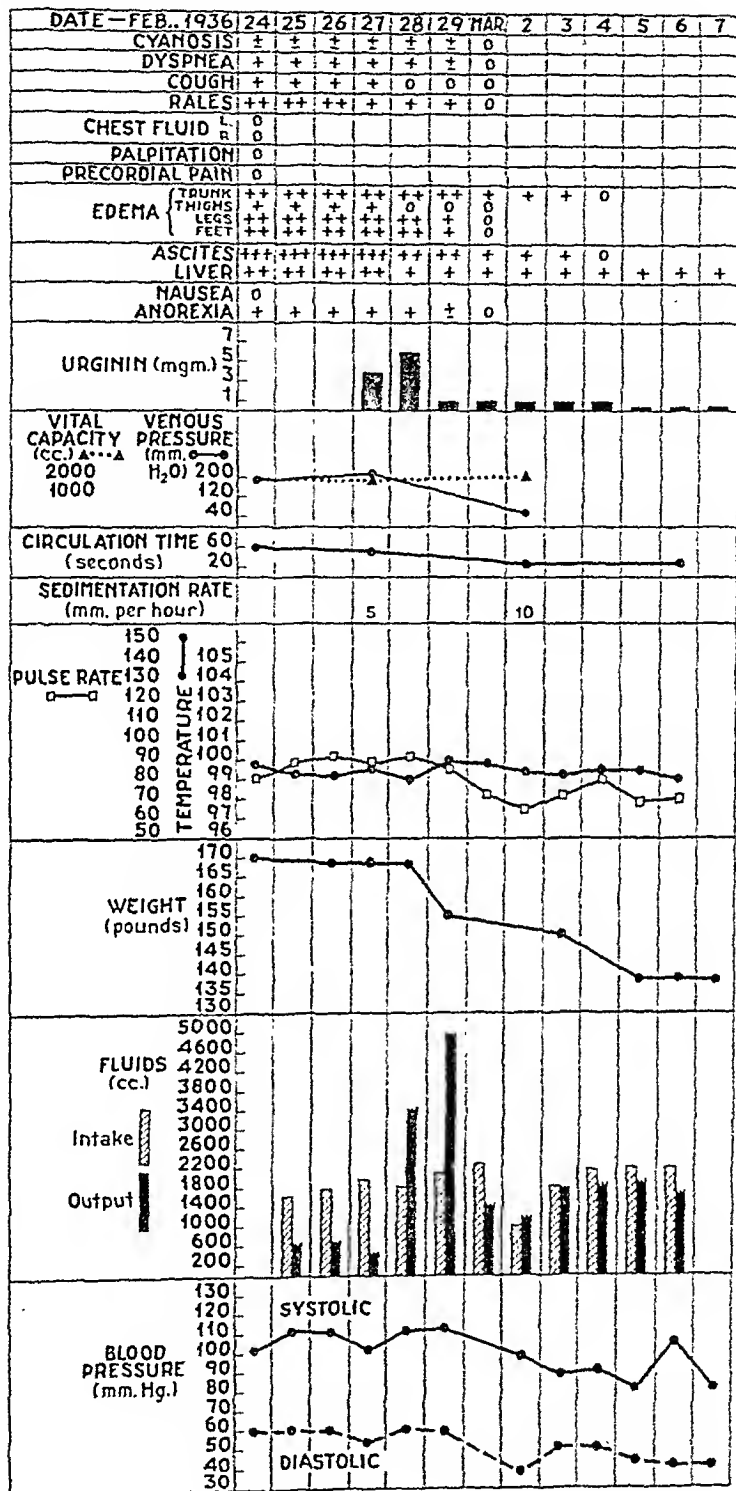


Fig. 4.—Advanced cardiac insufficiency in which there was no change in the picture during a control period of three days, during which no medication was given. Marked clinical improvement was induced by 10.0 mg. of urginin given in two days, followed by smaller maintenance doses. Venous pressure fell, vital capacity increased and circulation time became more rapid. The heart rate was slowed, although the rhythm was regular. There was tremendous diuresis and associated loss of weight. The level of arterial blood pressure, both systolic and diastolic, was lowered.

UNIT NO. 300783  
H.M.-FEMALE  
AGE-42 YEARS

**RHEUMATIC HEART DISEASE (INACTIVE)**  
**MITRAL STENOSIS and INSUFFICIENCY**  
**CARDIAC HYPERTROPHY AURICULAR FIBRILLATION**

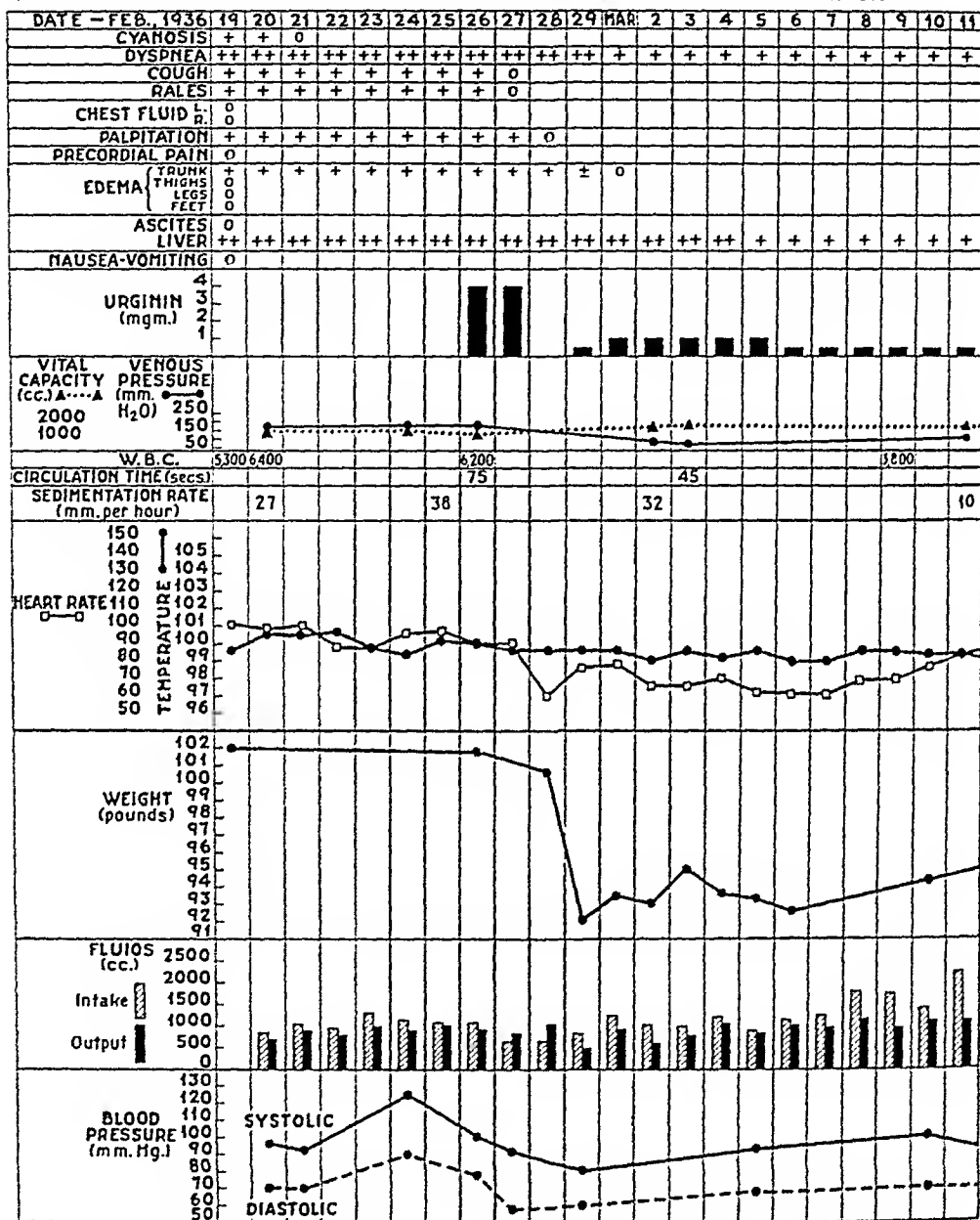


Fig. 5.—Moderately advanced cardiac insufficiency in which a control period of seven days rest in bed without medication was not followed by improvement. Although auricular fibrillation was present, the heart rate was not very rapid. Administration of 8.0 mg. of urginin in two days induced relief of symptoms and signs, slowed the ventricular rate, lowered venous pressure, increased vital capacity and accelerated circulation rate. There was marked and rapid loss of weight, unaccompanied by correspondingly large diuresis. It is probable that all of the urine was not collected and measured. Compensation was maintained by continued small doses of urginin.

lar rate fell from 10 to 70 beats per minute. In two patients with hyperthyroidism the drug did not appear to affect rate.

When edema was present, diuresis was the rule unless the patients were moribund or the heart was unresponsive to all therapeutic efforts. In patients without cardiac disease to whom the drug was given, no increase in urinary output occurred. Nine cases had persistent edema after partial improvement was brought about by urginin; all responded with large diuresis to intravenous injections of salyrgan or mercupurin. It appears that the two scillonins contained in urginin exert no specific stimulating effect on the kidneys. As is the case with digitalis, such diuresis as occurs in congestive heart failure is probably secondary to improvement in the renal circulation.

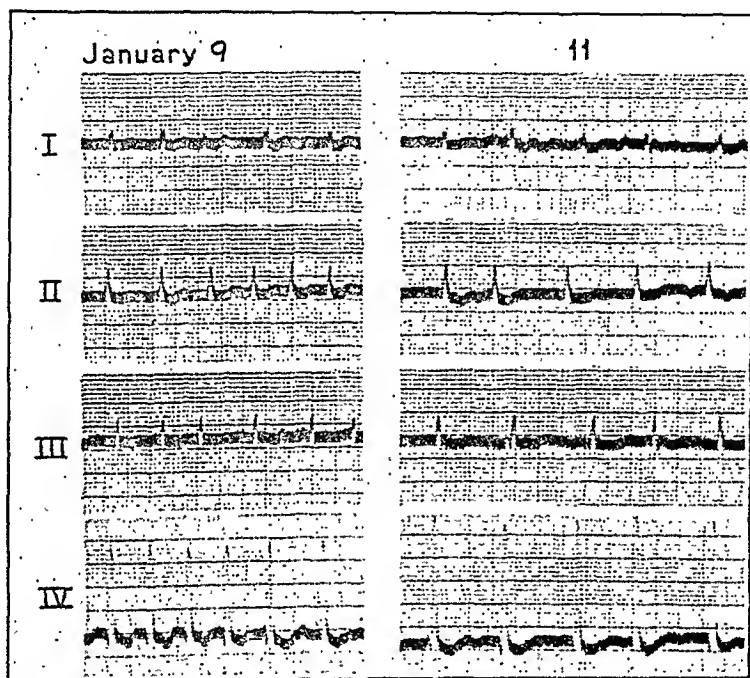


Fig. 6.—Slowing of ventricular rate and T-wave changes produced by urginin in a case of auricular fibrillation.

Unit No. 475409. Female, aged fifty-six years. Diagnosis: Arteriosclerosis; coronary sclerosis; cardiac hypertrophy; permanent auricular fibrillation; cardiac insufficiency (moderate).

January 9: Rate 160. After control record was taken, urginin 5.0 mg. was given. January 10: 5.0 mg. January 11: Rate 100; T<sub>1</sub> partly inverted; T<sub>2</sub> deeper.

One case of persistent auricular tachycardia, unresponsive to digitalis, did not show a change in rhythm after urginin.

Premature beats disappeared in 10 patients after treatment.

#### DOSAGE

The effective dose, that is, the amount necessary to bring about the optimal therapeutic result, was estimated on the basis of clinical observation and the effect on ventricular rate in cases of auricular fibrillation. In terms of cat units, it was a little more than twice that of digitalis. Thus, one tablet of urginin (0.5 mg. or 2.13 cat units) is not quite equivalent in therapeutic potency to one tablet of com-

mercial digitalis (0.1 gm.) when the latter is assayed to equal one cat unit. For clinical purposes, 0.5 mg. of urginin may be regarded as equal in therapeutic efficacy to 0.1 gm. of a preparation of digitalis standardized in this manner. In other words, approximately two cat units of urginin, orally administered, are required to induce the same effects as one cat unit of digitalis. This difference in the two drugs, between the potency established by biologic assay and that observed clinically, is due probably to less complete absorption or more rapid elimination in the case of urginin.

The *total effective dose* was calculated by subtracting from the full amount given, the quantity theoretically excreted each day. It ranged, in different patients, from 6.5 to 14.0 mg., with an average of 9.0 mg. (18 cat units). Similar variations in digitalis dosage are commonly seen, depending on the etiology of the cardiac lesion, the degree of cardiac insufficiency and on individual idiosyncrasy.

The *daily maintenance dose* was determined by observing the amount required to keep the ventricular rate at a given level in cases of auricular fibrillation; or, in the presence of sinus rhythm, to maintain changes in the form of the electrocardiogram after these had appeared. In cases of cardiac insufficiency with auricular fibrillation, it ranged from 0.5 to 2.0 mg., with an average of 1.05 mg. The average for cases with hyperthyroidism was 1.22 mg., while for those with normal metabolic rates it was 0.89 mg. In the cases with sinus rhythm, it ranged from 0.5 to 1.5 mg., with an average of 0.95 mg. The average daily maintenance dose for all cases, excluding those with hyperthyroidism, was 0.92 mg.

The effective dose was given over periods varying from one to six days. Large, single doses often caused nausea or indigestion; after this became apparent, they were avoided unless advanced congestive failure demanded rapid relief. A satisfactory scheme of dosage was to give 1.5 mg. (3 tablets) three times daily after meals for two days; 1.0 mg. (2 tablets) twice daily until the desired effects were produced; then 0.5 mg. (1 tablet) twice daily as a maintenance ration. The plan was modified as circumstances required.

*Rectal Administration.*—After trial in two cases, the method was abandoned because of the local irritating action. The clinical result indicated that the drug was absorbed. It is possible that a preparation suitable for rectal use can be made.

#### DETERMINATION OF EFFECT

This was variable. It was calculated by giving large initial doses on one or two days, then discontinuing the drug and observing the length of time necessary for the disappearance of changes in the form of the electrocardiogram (T-waves and R-T or S-T segments). It was estimated also in cases of auricular fibrillation by noting the interval

which elapsed between the last dose of urginin and the beginning of an increase in ventricular rate. The time varied, obviously, with the total amount in the body and hence with the size of the dose and the speed of its administration. Changes in the form of the electrocardiogram were observed as long as seventeen days after stopping the drug (Figs. 7 and 8 show their persistence for eleven and twelve days). Prolonged A-V conduction was recorded from seven to sixteen days after the last dose was given. In cases of auricular fibrillation, the effect on heart rate began to diminish in from three to ten days; it completely disappeared in from eight to eleven days.

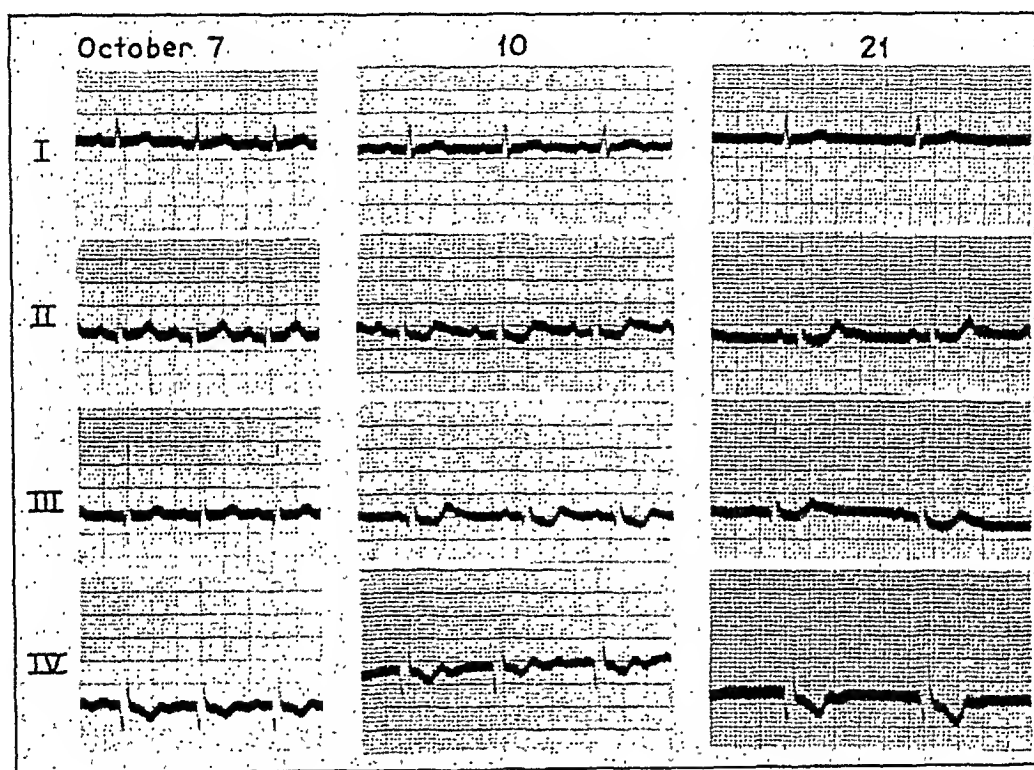


Fig. 7.—Persistence of effect of urginin on the electrocardiogram eleven days after its administration was discontinued.

Unit No. 311367. Male, aged thirty-three years. Diagnosis: Tuberculous peritonitis with ascites. (No cardiac disease.)

October 7: Control: rate 95; P-R 0.16 sec. Urganin 1.5 mg. October 8: 4.5 mg. October 9: 4.5 mg. October 10: Rate 75; P-R 0.17 sec. Record shows slowing of rate and partial inversion of  $T_2$  and  $T_3$ ;  $T_4$  partly upright. Urganin 3 mg. October 21: Eleven days after last dose. Rate 60; P-R 0.16 sec. R- $T_1$  and R- $T_2$  still depressed;  $T_4$  inverted.

#### TOXIC EFFECTS

In six patients, nausea and vomiting occurred soon after urginin was taken. Four of these were nauseated and unable to take other medication by mouth before the drug was given. Digitalis was subsequently administered to three of them and caused nausea and vomiting in each. Every patient without previous nausea was able to retain urginin if given after a meal in amounts not exceeding 1.5 mg. (3 tablets) at a time. In nine additional patients, nausea without vomiting was complained of immediately after taking the drug; in



each instance, smaller doses were tolerated without distress. Two patients had diarrhea, which ceased during continued urginin medication. Two complained of dizziness and flushing.

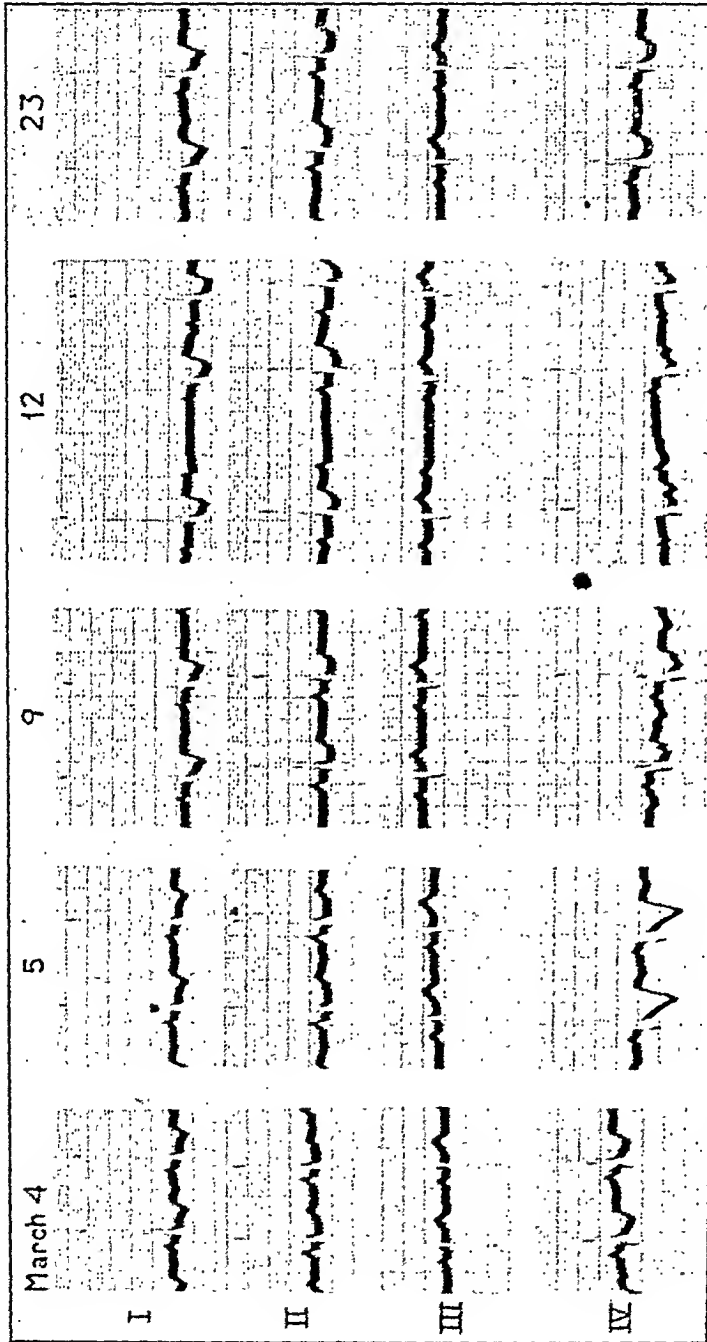


Fig. 8.—Incomplete heart-block and T-wave changes produced by urginin; persistence of latter for twelve days after the drug was discontinued.  
 Unit No. 48087a. Male, aged forty-five years. Diagnosis: Hypertension; arteriosclerosis; cardiac hypertrophy; arteriolar nephrosclerosis.  
 March 4: Control; rate 75; P-R 0.15 sec. March 5: Urginin 9.5 mg. Record taken after 3.0 mg. were given. T<sub>1</sub> higher; T<sub>2</sub> deeper. March 6, 7, and 8: 2.0 mg. March 9: Rate 70; P-R 0.18 sec. T<sub>1</sub> more deeply inverted; R-T<sub>2</sub> depressed; T<sub>2</sub> diphasic and notched. Urginin 2.0 mg. March 10 and 11: Urginin 2.0 mg. On the 11th, nausea and vomiting. March 12: Incomplete heart-block with more marked T-wave changes. March 23: Twelve days after urginin was discontinued; sinus rhythm, rate 65; P-R 0.19 sec. There are still changes in the form of the T-waves and R-T segments.

One patient, nauseated by digitalis, took urginin without complaint. Another had diarrhea after taking digitalis, but none following urginin therapy.

One patient became mentally confused and had delusions of persecution after 16.5 mg. had been given during a period of eight days.

There were no changes in the electrocardiogram or other symptoms suggesting poisoning by urginin. The psychic state returned to normal several days after the drug was discontinued.

In two instances transient auricular fibrillation appeared, and in three, auriculoventricular nodal rhythm was noted following dosage which was not regarded as excessive. One case of incomplete heart-block was converted to complete block, reverting to the former rhythm three days after urginin was stopped.

To one patient, 19.0 mg. (38 tablets, containing about 81 cat units) were given intentionally over a period of seven days (Fig. 8). Vomiting and incomplete heart-block occurred simultaneously at the end of this time. Two additional tablets of 0.5 mg. each given on the following day did not cause the block to become complete, and no premature beats were observed. After the drug was stopped, vomiting continued for two days and nausea for three days. Changes in the form of the electrocardiogram persisted for at least twelve days.

Premature contractions were conspicuously absent as evidence of urginin intoxication.

No deaths could be attributed to the action of urginin.

#### EFFECTS ON THE ELECTROCARDIOGRAM

These were similar to the ones known to be produced by digitalis.<sup>16</sup> The changes observed were on rate, T-waves, R-T, and S-T segments, and on auriculoventricular conduction time. To six patients, comparable doses of urginin and of digitalis were given in succession. No appreciable differences were noted in the character of the changes produced in serial records.

In one case of auricular flutter, the auricular rate was slowed but the rhythm was not altered. Prolongation of the P-R interval was produced in six patients, incomplete A-V block in two, and complete A-V block in one. There was no effect on intraventricular conduction.

In ten patients, premature beats disappeared after medication. In eight instances these were ventricular, in one auricular, and in one junctional in origin.

#### SUMMARY AND CONCLUSIONS

1. A clinical study was made of the effects of urginin on 62 patients in the wards of the hospital. In those with cardiac insufficiency, urginin, administered orally, exerted an action on the heart like that of digitalis. The signs and symptoms of congestive failure tended to disappear. As a rule, edema, when present, was lost and diuresis occurred. The venous pressure fell, the circulation time decreased and the vital capacity was increased. These effects were noted in the presence of regular rhythm as well as when the auricles were fibrillating.

2. In cases of auricular fibrillation, the ventricular rate was slowed; when the rhythm was regular, slowing occurred in about one-half of the cases.

3. Diuresis and loss of weight did not occur in the absence of congestive failure.

4. The therapeutic potency of urginin, in terms of cat units, was about one-half that of digitalis. Thus, approximately two cat units of urginin were required to induce effects, both therapeutic and toxic, comparable to those induced by one cat unit of digitalis. This difference in activity may be ascribed to less complete absorption or more rapid elimination in the case of urginin.

5. A satisfactory scheme of dosage, when no digitalis or urginin had been given for at least ten days preceding, was: 1.5 mg. (3 tablets) three times a day after meals for two days; 1.0 mg. (two tablets) twice daily until the desired effects were produced.

6. The daily maintenance dose ranged from 0.5 to 2.0 mg. The average was 0.92 mg. (approximately two tablets of 1.0 mg.).

7. The total effective dose (the full amount given less 1.0 mg. theoretically excreted each day) ranged from 6.5 to 14.0 mg. The average was 9.0 mg. (18 cat units).

8. The duration of effect after therapeutic doses was variable. In cases of auricular fibrillation, the effect on ventricular rate began to diminish in from three to ten days. It disappeared completely in from eight to eleven days. Changes in the form of the electrocardiogram were observed for as long as seventeen days after the drug was discontinued. Prolonged A-V conduction was recorded from seven to sixteen days after the last dose.

9. In 6 of 62 patients, nausea and vomiting occurred soon after urginin was taken. Every patient without previous nausea was able to retain urginin if given after a meal in amounts not exceeding 1.5 mg. (three tablets). In nine additional patients, nausea without vomiting occurred; in each instance smaller doses were tolerated without distress. Other toxic effects noted were diarrhea (two cases), dizziness and flushing (two cases), mental confusion (one case), transient auricular fibrillation (two cases), auriculoventricular nodal rhythm (three cases), prolonged P-R interval (six cases), and A-V heart-block (three cases).

10. Premature beats as evidence of intoxication were not observed.

11. One patient, nauseated by digitalis, took urginin without distress. Another had diarrhea after taking digitalis, but none following urginin therapy.

12. The occurrence of any of the symptoms or signs of intoxication affords an indication for immediate cessation of therapy.

13. No deaths could be attributed to the action of urginin.

14. The effects on the electrocardiogram were similar to those seen after digitalis. The alterations noted were in the T-waves, R-T, or S-T segments, and on A-V conduction.

15. In ten patients, premature beats disappeared after medication.

16. Urginin is an effective cardiac remedy. It offers no advantages over digitalis with respect to its action in myocardial insufficiency. But it serves a purpose in that occasionally, patients in whom digitalis induces nausea, vomiting, or diarrhea are able to take urginin without suffering from unpleasant symptoms. It may be useful also when a patient harbors an unfounded prejudice against the use of digitalis.

## REFERENCES

1. Sharp, G.: Squill Studied Historically, *Pharmaceut. J. and Pharmacist*. 30 (4th series): 136 and 170, 1910.
2. Scheer, H., and Sigerist, H. E.: Zur Geschichte der Scilla Verwendung, *Schweiz. med. Wchnschr.* 57: 1168, 1927.
3. Hirschfeld, E.: Studien zur Geschichte der Heilpflanzen. 2. Scilla, *Kyklos* (Jahrb. des Inst. f. Geschichte der Med. a. d. Univ. Leipzig) 1: 163, 1928. (An excellent historical review.)
4. Van Swieten, G. L. B.: *Commentaria in Hermannii Boerhaave Aphorismos de Cognoscendis et Curandis Morbis*, Leyden, Bd. 4, 1764.
5. Home, F.: *Clinical Experiments, Histories and Dissections*, Edinburgh and London, 1780, J. Murray and William Creech, p. 357.
6. Ref. 1, p. 137. This statement is quoted from a letter from Professor Alexander Monroe, Edinburgh, to Mrs. Thrale. It should be remembered that in Johnson's day, the pint contained 12 fluid ounces.
7. Withering, W.: *An Account of the Foxglove and Some of Its Medical Uses: With Practical Remarks on Dropsy and Other Diseases*, Birmingham, 1785, M. Swinney.
8. Fagge, C. H., and Stevenson, T.: On the Application of Physiological Tests for Certain Organic Poisons and Especially Digitaline, *Proc. Roy. Soc.* 14: 270, 1865.
9. Dixon, W. E., and Haynes, G. S.: The Biochemical Standardization of Drugs, *Med. Magazine* 15: 25, 1906.
10. Mendel, F.: Bulbus Scillae, ein zu Unrecht vernachlässigtes Herzmittel, *Therap. d. Gegenwart*. 59 (Neueste Folge 20): 16, 50, 92, and 126, 1918.
11. Stoll, A.: *The Cardiac Glycosides*, London, 1937, The Pharmaceutical Press, p. 27.
12. Dyas, C. S.: Method of Extracting Cardio-Active Principles of Squill, U. S. Patent No. 1,972,876, Sept. 11, 1934. Also, Ingersoll, A. W.: Analytical Report for Grisard Laboratories (Unpublished).
13. Robinson, G. C.: The Therapeutic Use of Digitalis, *Medicine* 1: 1, 1922.
14. Sollmann, T.: *A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology*, 5th Ed., Philadelphia, 1936, W. B. Saunders Company.
15. Carr, J. G., and Mayer, J. D.: Clinical Experience With a Derivative of Squill, *Arch. Int. Med.* 56: 700, 1935.
16. Maher, C. C., and Sittler, W. W.: The Effect of Two Water-Insoluble Squill Glucosids Upon the Electrocardiogram, *Am. J. M. Sc.* 192: 41, 1936.
17. Results obtained in the Laboratory of Pharmacology in the University of Chicago, under the direction of Dr. H. B. Van Dyke, and supplied to us by the Calco Chemical Co., Inc.
18. New and Nonofficial Remedies, 1936, *Am. Med. Assn.*, p. 179.
19. Wallace, E. W., and Van Dyke, H. B.: Cumulative Poisoning by Squill Derivatives and by Ouabain, *J. Pharmacol. and Exper. Therap.* 48: 430, 1933.

# THE EFFECT OF THEOPHYLLINE WITH ETHYLENEDIAMINE (AMINOPHYLLINE) ON THE COURSE OF CARDIAC INFARCTION FOLLOWING EXPERIMENTAL CORONARY OCCLUSION\*

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NEW YORK, N. Y.

CONSIDERABLE evidence now exists that the xanthines, namely, caffeine, theobromine, and theophylline, dilate the coronary vessels and increase the coronary blood flow. This general conclusion has been derived from studies with several species of animals, the cat, dog, and rabbit, and from various types of experiments, namely, isolated strips of blood vessel,<sup>1, 2</sup> perfusion experiments with the isolated heart,<sup>3, 4</sup> heart-lung preparations,<sup>5</sup> and studies of coronary blood flow in the anesthetized animal.<sup>6</sup>

In perfusion experiments, very dilute solutions of the xanthines fail to cause coronary vasodilatation. The increase in the coronary flow seen in cases in which the drug is injected intravenously is of short duration,<sup>6, 7</sup> lasting only from a few minutes to about one-half an hour, corresponding to the period of the relatively high concentration of the drug in the blood stream.<sup>8</sup> The concentration in the blood stream after the intramuscular injection does not rise as high as directly after the intravenous injection, and as far as we know, the effect on the coronary flow of the xanthines administered orally or intramuscularly has not been determined. There is the suggestion in the recent experiments of Wiggers and Greene<sup>9</sup> that changes in the total coronary inflow and outflow are not necessarily accompanied by similar changes in the collateral flow to an infarcted area. None of the experimental studies on coronary flow is free of objections as evidence for the conclusion that the xanthines produce an increase in the volume of capillary flow in the heart. However, these results have served as the experimental basis on which the xanthines are advocated in the treatment of disease of the coronary arteries.

In 1935 a paper was published by Fowler, Hurevitz, and Smith<sup>10</sup> in which they reported that the daily oral administration of theophylline with ethylenediamine (aminophylline) in doses approximating those used therapeutically† reduces the size of the infarct resulting from the ligation of a coronary artery in the dog. They declared that clinical experience<sup>11</sup> was in accord with these findings<sup>10</sup> and suggested the use of this drug in patients with coronary thrombosis.

\*From the Department of Pharmacology of Cornell University Medical College.

†Their doses were 3 grains daily for a dog. The weights of the dogs were not stated, and on the basis of 10 to 20 kg., the dose was equivalent to about 10 to 20 grains for a man.

The suggestion that aminophylline might reduce the size of a myocardial infarct is extremely important, and their results are strongly indicative of a beneficial influence of the xanthine. The present study was undertaken to explore the possibilities further, and as a matter of practical significance, to determine whether the influence of aminophylline on the size of the infarct is a phenomenon peculiar to the dog or is applicable to other species as well. The effect of aminophylline was studied on the course of myocardial infarction resulting from coronary ligation in the cat. In this study a larger series of animals was employed, an infarct was produced the size of which could be accurately measured, and the work was carried out under conditions which excluded the possible influence of subconscious bias in the comparison of the results in control and treated animals.

The coronary circulations of the cat and the dog are essentially similar in that, in both there are extensive anastomoses between the coronary arteries and, also in both, the xanthines produce an increase in the coronary flow in perfusion experiments. Nevertheless, as will be seen, in contrast to the results reported for the dog, the xanthines were without influence on the course of the myocardial infarction in the cat.

#### METHOD

Various coronary arteries were ligated in 65 cats, namely, the right coronary, the descending branch of the left at various levels, the circumflex branch of the left, and also the right together with one or another of these two branches. The infarcts which proved most satisfactory for measurement resulted from ligation of the circumflex branch of the left coronary. This vessel was ligated in 52 animals, and the effect of aminophylline on the size of the infarct resulting from this operation alone was studied.

*Operative Technique.*—The animals were anesthetized with ether. The ether was supplied by means of a metal catheter passed through the mouth into the trachea, and through this also artificial respiration was maintained by interrupted positive pressure insufflation.

The operation was performed aseptically, tincture of iodine being used for the skin sterilization. An incision 3 to 4 cm. long was made in the left third or fourth intercostal space beginning about 0.5 cm. from the sternum. The pericardium was incised over the region of the left auricular appendage, which was held to one side to expose the left coronary artery. This was isolated at the point of its bifurcation into the descending and circumflex branches. A silk ligature was passed by means of a fine needle, and tied, around the circumflex branch at its junction with the left common coronary artery. The veins were not included in the ligature. The incision in the pericardium was left open. The thorax was closed with silk ligatures in two or three layers.

The complete operation for ligation of the left circumflex artery, from the opening to the closure of the thorax, took an average of 16.2 minutes in a series of 50 animals, with variations from 8 to 43 minutes.

Skin sutures were removed usually on the fifth day, occasionally on the fourth, sixth, or seventh day.

*General Routine.*—Comparable conditions for the animals of the treated and of the control series were insured by assigning to each of the two groups an approximately equal number of animals operated upon on the same day.

Daily observations were made regarding the general condition of the animal, the amount of food eaten, and the condition of the wound. The diet consisted of evaporated milk, raw chopped meat, and a canned mixed food. The animals were weighed before the operation, occasionally during, and at the end of the subsequent three-week period. An electrocardiogram was taken just prior to the operation, immediately after its completion, the following day, then every third day, and finally at the end of the experiment. At this time the blood pressure was recorded with a mercury manometer by means of a cannula inserted in the carotid artery (during local anesthesia).

Distemper was prevented by a prophylactic dose of 5 c.c. of canine antidistemper serum, injected subcutaneously at the time of operation (in 9 treated and in 9 control cats). In all but one of the remaining animals, symptoms of distemper were controlled by the injection of one or more doses of 5 c.c. of the antidistemper serum (in 4 treated and in 6 control cats).

At the end of the experiment, the animals were killed by the intravenous injection of digitalis, in order to determine the toxicity of digitalis in the presence of a myocardial infarct. The results of these observations are presented in another report.<sup>12</sup>

*Treatment With Aminophylline.*—Theophylline with ethylenediamine (aminophylline) in a 10 per cent solution was administered daily in one dose. Most of the animals received 25 mg. per kg. (calculated on the basis of the body weight before the operation) by intramuscular injection for twenty consecutive days, the initial dose being given within a few minutes after the operation. There were a few exceptions to this general plan. The first dose was 10 mg. per kg. by intravenous injection in each of two cats; in four cats the daily dose by intramuscular injection was reduced to 10 mg. per kg. during the course of treatment, so that two received 17 doses of 10 mg. per kg., one received 15 such doses, and one, two such doses.

These doses of aminophylline appeared to produce no change in the general behavior of the animal that might indicate poisoning. The toxicity of the 10 per cent solution of aminophylline was tested by intramuscular injection in several normal cats. In each of three, a dose of 50 mg. per kg. produced no appreciable effects after 16 consecutive

daily doses. A dose of 100 mg. per kg. caused vomiting, and death with convulsions after the sixth consecutive daily injection. In each of two animals, a dose of 150 mg. per kg. caused nausea and vomiting, and death after several hours.

The injections were made into the thigh muscles, using right and left alternately. The thigh muscles were sectioned post-mortem and examined for signs of irritation or infection. These appeared normal in all but one animal, in which a deep abscess had developed, first noted on the eighth day.

*Post-mortem Examinations.*—These were made in all cases.

The location of the ligature was established. In this way two errors were discovered in which the left common artery had been ligated, causing death within a few minutes.

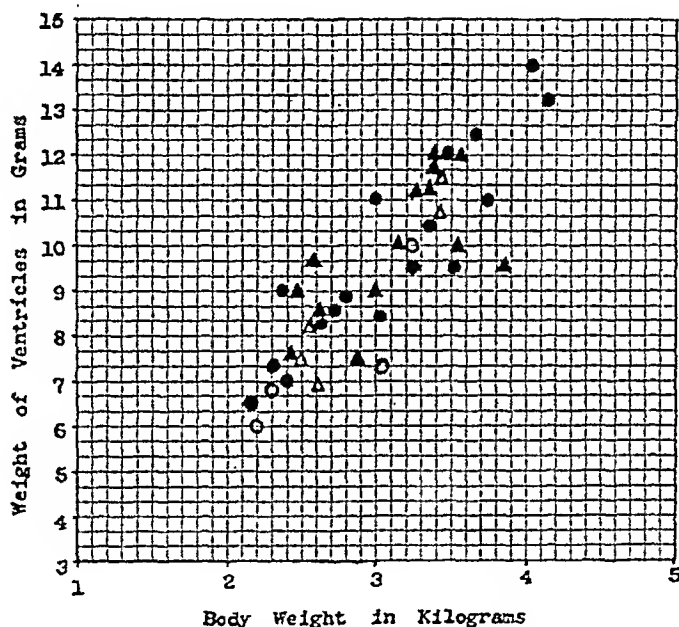


Fig. 1.—Correlation of weight of body with weight of ventricles. ▲ (treated; survived twenty-one days); △ (treated; died before twenty-one days); ● (control; survived twenty-one days); ○ (control; died before twenty-one days).

Soft adhesions often bound the margins of the incision in the pericardium partly or completely to the left auricular appendage. There were no pericardial effusions.

In no case were there adhesions between the parietal and visceral pericardium or any gross signs of pericarditis over the area of the infarction.

Intramural thrombi were absent even in cases of very extensive infarction.

The parietal pericardium, the aorta, pulmonary artery, and auricles were cut away, and the ventricles were weighed. A definite correlation between the body weight and weight of the ventricles was found to exist (Fig. 1).



After the infarct was measured, the heart was fixed in formalin and frozen sections from several areas were stained with hematoxylin and eosin for microscopic examination.

Serious secondary infection did not occur. Of the 42 cats used as the basis for this study, mild secondary infections at the site of the wound occurred in 12 animals (in four treated animals and eight controls). Stitch abscesses only were present in nine of these, and had completely healed before the end of the experiment.

*Coronary Circulation in the Cat.*—In each case the right and left coronary arteries and their main branches were dissected out, their relative sizes noted, and a sketch was made of their distribution, especially on the posterior wall of the heart. Usually the left circumflex artery was larger than the right circumflex. The left circumflex usually was found to give off one or more branches on the anterior wall of the left ventricle, then turn posteriorly and run across the upper border of the left ventricle, giving off in its course several branches to the auricle and to the posterior wall of the left ventricle, with its terminal branches lying close to the interventricular sulcus on the posterior surface of the heart. Sometimes the terminal branches extended for a considerable distance into the wall of the right ventricle. On the other hand, occasionally the right circumflex vessel was very much larger than the left, and sent branches to supply a fairly large portion of the posterior wall of the left ventricle. Marked differences in the size of the infarcts could often be directly related to manifest differences in the relative size of the right and left circumflex vessels. For example, in one animal, ligation of the right coronary artery produced a small infarct involving only the posterior wall of the left ventricle midway between the base and the apex. In this case the right coronary artery supplied most of the posterior wall of the left ventricle, and the left circumflex vessel was exceedingly small.

Fig. 2 shows a sketch of the circulation and the infarct in the average animal.

*The Infarct.*—The infarct was examined before and after the chambers of the heart were opened. After ligation of the left circumflex artery, the location and form of the infarct were fairly uniform, although the size varied considerably. It involved chiefly the posterior wall of the left ventricle, and all layers of the wall. It was irregularly triangular in shape with the base along the auriculoventricular border. It narrowed toward the apex, terminating above the posterior surface of the apex in the average-sized infarct, and involved the posterior papillary muscle. In the larger lesions, the infarct extended around to the anterior surface of the apex, to the anterior papillary muscle, along the posterior border of the septum, and in seven cases it involved a narrow strip of the right ventricle adjacent to the involved septum.

The infarct was readily recognized by the color and the thinning of the ventricular wall. Infarcted areas about a week or ten days old were fairly thick, yellow, and inelastic. Those about three weeks old showed marked thinning of the wall and atrophy of the papillary muscle; they were reddish and slightly lighter in color than the surrounding musculature, and, usually, showed some yellowish mottling. The boundary was less distinct in the older infarcts, although in all it was fairly clearly defined.

*Measurement of Infarct.*—The boundaries of the infarct were often more clearly defined and somewhat larger on the endocardial surface of the ventricle than on the outer surface. The opened ventricle was laid out flat, the area of the infarct outlined in India ink on the endo-

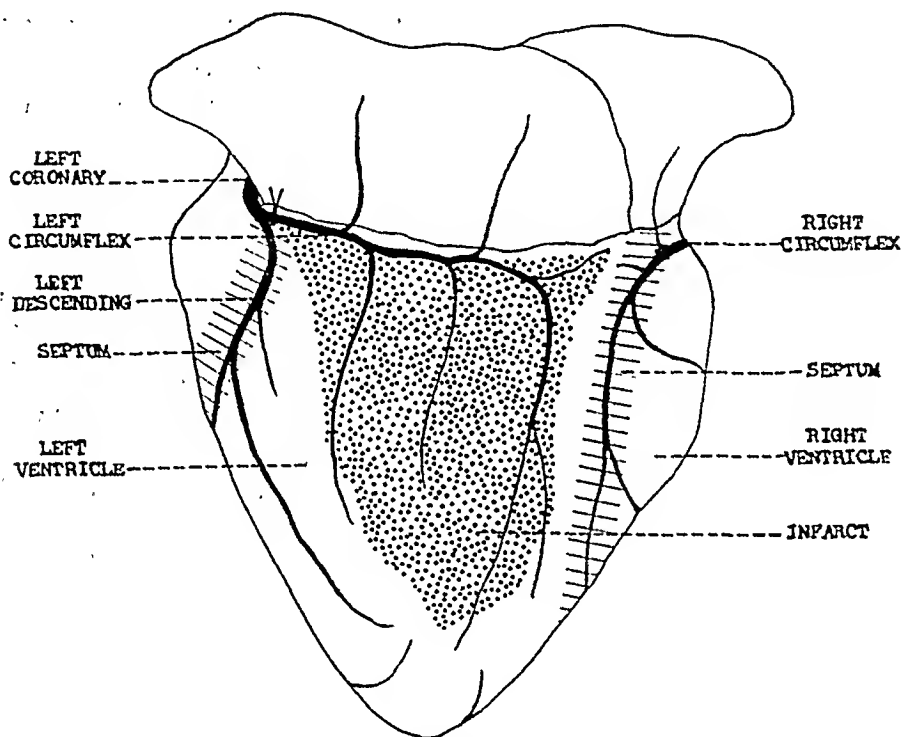


Fig. 2.—Dorsolateral view of heart. Note usual coronary circulation, site of ligation on left circumflex artery, and location, size, and shape of average infarct.

cardial surface, and a contact tracing of the area was made on a ground glass plate. In some cases a contact reproduction of the inked outline on the heart was made directly on tracing paper, and in still others, a direct contact paper cut was made. The areas of the infarcts, reproduced independently by two workers using the same specimen, agreed within 8 per cent. An estimate of the relative sizes of the infarcts was made by inspection, and the exact size of the tracings or cuts was measured by the planimeter.

An attempt was made to correlate the weight of the ventricles with the size of the infarct. No definite relationship was revealed by this relatively small series. The scatter of the points, however, was found to be essentially similar in the control and the treated groups (Fig. 3).

TABLE I

CAUSE OF DEATH IN 21 ANIMALS THAT FAILED TO SURVIVE THE THREE-WEEK PERIOD  
AFTER LIGATION OF THE LEFT CIRCUMFLEX ARTERY

| DURATION OF LIFE<br>AFTER LIGATION | NO.<br>CATS | CAUSE OF DEATH                   | REMARKS  |
|------------------------------------|-------------|----------------------------------|--|
| A few minutes                      | 1           | Hemorrhage                       | Tear in myocardium   |
| A few minutes to<br>a few hours    | 9           | Acute effects of in-<br>farction | Unusually large vessel   |
| 5 to 14 days                       | 6           | Pneumonia                        | One unusually large infarct; others<br>of average size                                     |
| 18 days                            | 1           | Distemper                        |  |
| 6 days                             | 1           | Cardiac failure?                 | Pulmonary edema, peritoneal and<br>pleural serosanguineous effusion;<br>very large infarct |
| 8 days                             | 1           | Cardiac failure                  | Subcutaneous edema; pleural and<br>peritoneal effusions; very large<br>necrotic infarct    |
| 4 days                             | 1           | Ether                            | During operation on infected foot  |
| 8 days                             | 1           | Undetermined                     | Infarct of average size  |

TABLE II

RESULTS IN ANIMALS TREATED WITH AMINOPHYLLINE AND IN CONTROLS WHICH  
SURVIVED THREE WEEKS AFTER LIGATION OF LEFT CIRCUMFLEX ARTERY

|   | CONTROL GROUP                           | TREATED GROUP                           |
|---|---|---|
| Number of cats  | 17                                      | 14                                      |
| Averages for groups   |   |   |
| Initial body weight   | 3.12 kg.<br>(2.15-4.15)                 | 3.09 kg.<br>(2.40-3.55)                 |
| Duration of operation   | 14.0 min.<br>(8-43)                     | 19.2 min.<br>(10-22)                    |
| Loss of body weight   | 11.8%<br>(Loss of 34.9—<br>gain of 7.2) | 13.0%<br>(Loss of 33.3—<br>gain of 7.3) |
| *Mean blood pressure  | 156 mm.<br>(133-183)                    | 145 mm.<br>(120-170)                    |
| Weight of ventricles  | 9.9 gm.<br>(6.5-14.0)                   | 9.9 gm.<br>(7.5-12.0)                   |
| Size of infarct   | 0.82 sq. in.<br>(0.35-1.47)             | 0.95 sq. in.<br>(0.45-2.00)             |
| R-T segment displacement  |   |   |
| Marked  | 64.7%                                   | 64.3%                                   |
| Doubtful  | 23.5%                                   | 21.4%                                   |
| None  | 11.8%                                   | 14.3%                                   |
| Per cent of those with marked dis-<br>placement which disappeared be-<br>fore three weeks | 45.4%                                   | 44.4%                                   |
| Average duration of displacement in<br>those returning to normal before<br>three weeks    | 16.4 days                               | 15.5 days                               |
| Degree of healing of infarct on micro-<br>scopic examination                              |   |   |
| Advanced  | 18.8%                                   | 7.7%                                    |
| Moderate  | 56.2%                                   | 61.5%                                   |
| Slight  | 25.0%                                   | 30.8%                                   |

\*Averages based on 12 cats in each group.

*Blind Test.*—The blind test was applied to that part of the work which involved judgments. The description of the animal's appearance at the end of the three-week period was made by one to whom the identity of the animal as a control or one which had received aminophylline was unknown. The outlining of the area of the infarct and its reproduction, as well as the classification of the microscopic sections, were also conducted under similar conditions.

### RESULTS

Of the 52 animals in which the circumflex branch of the left coronary was ligated, 9 died of the acute effects of the infarction, and 12 died of other causes in less than three weeks. The causes of death in these are presented in Table I.

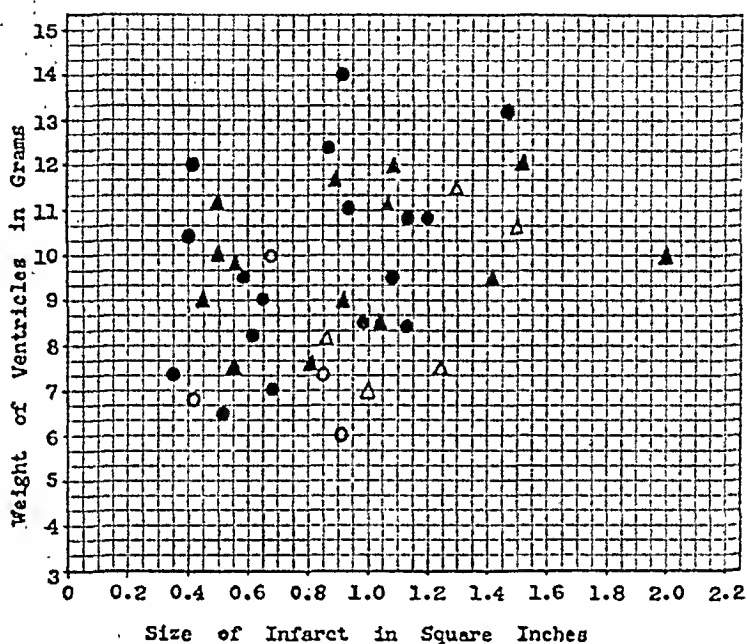


Fig. 3.—Lack of correlation of size of infarct with weight of ventricles. Symbols are as in Fig. 1.

Table II shows the results obtained in 31 animals which survived the three-week period. Of these, 17 served as controls and 14 were treated with aminophylline. The two groups are almost identical in respect to those factors which might have a bearing on the size of the resulting infarct, namely, the general condition of the animal, the body weight, the weight of the heart, the state of the animal's nutrition as judged by the change in body weight, and the blood pressure.

The average body weight at the beginning was 3.12 kg. in the controls, and 3.09 kg. in the treated group. The majority of the animals were indistinguishable from normal and some weighed more at the end of the three-week period than at the start. The average change was a loss of 11.8 per cent of the original body weight in the controls and 13 per cent in the treated series.

The mean blood pressure averaged 156 mm. of mercury in the control series, and 145 mm. in the treated series.

The average weight of the heart was 9.9 gm. in both groups.

The average size of the infarct was 0.82 square inches in the control, and 0.95 in the treated group. Those treated with aminophylline, therefore, had developed an infarct which on the average was 18.3 per cent larger than those which had not received the drug. This difference would be increased if the area of involvement of the right ventricle had been included. This area, present in three of the treated group and in one of the controls, could not be measured on the endocardial surface of the heart by the method we employed. It is difficult to understand how aminophylline could have acted to make matters worse, and it is possible that a difference of this magnitude may be accidental.

The eleven animals which survived the operation but died before the end of the three-week period showed essentially similar results (Table III).

TABLE III

RESULTS IN ANIMALS TREATED WITH AMINOPHYLLINE AND IN CONTROLS WHICH LIVED MORE THAN TWENTY-FOUR HOURS, BUT DIED BEFORE THREE WEEKS

|                       | CONTROL GROUP               | TREATED GROUP               |
|-----------------------|-----------------------------|-----------------------------|
| Number of cats        | 6                           | 5                           |
| Averages              |                             |                             |
| Duration of life      | 9.5 days<br>(4-17)          | 7.6 days<br>(5-12)          |
| Body weight           | 2.64 kg.<br>(2.27-3.23)     | 2.91 kg.<br>(2.57-3.43)     |
| Duration of operation | 18.5 min.<br>(8-34)         | 13.0 min.<br>(10-17)        |
| Weight of ventricles  | 7.5 gm.*<br>(6.00-10.0)     | 8.6 gm.<br>(6.9-11.5)       |
| Size of infarct       | 0.82 sq. in.<br>(0.41-1.14) | 1.18 sq. in.<br>(0.87-1.50) |

\*The ventricles were weighed in only 4 animals of this group.

An analysis of the electrocardiograms was made and some of the results are summarized in Table II. Changes in the T-waves were not considered reliable, because they occur spontaneously in unanesthetized cats,<sup>12</sup> and were seen quite frequently in a series of animals in which the same operation was performed except for the ligation of the coronary artery, in connection with another study. Prolongation of conduction time above the control (amounting to 0.03 second or more) occurred\* in 8 of the 23 controls and in 5 of the 19 treated animals. These changes usually appeared immediately after the operation, although in some cases they were not present until a day or two later, and in all cases they were transient. The significance of the changes in conduction is uncertain under the conditions of these experiments. The tracings of the treated and of the control groups were compared with regard to displacements of the R-T segments and the incidence of ventricular tachycardia. The

\*Animals of Tables II and III are considered in these figures.

chief change of the R-T segment was elevation\* above the base line in all three leads or in Leads II and III only, and in all cases in which it occurred it was present immediately after the operation. The frequency of an elevated R-T segment seen postoperatively before any treatment, was substantially the same in both groups, namely, about 88 per cent of the control group and 86 per cent of the group which was to be treated, and the degree of elevation was also similar in both (Table II). Aminophylline, 10 mg. per kg., injected intravenously in

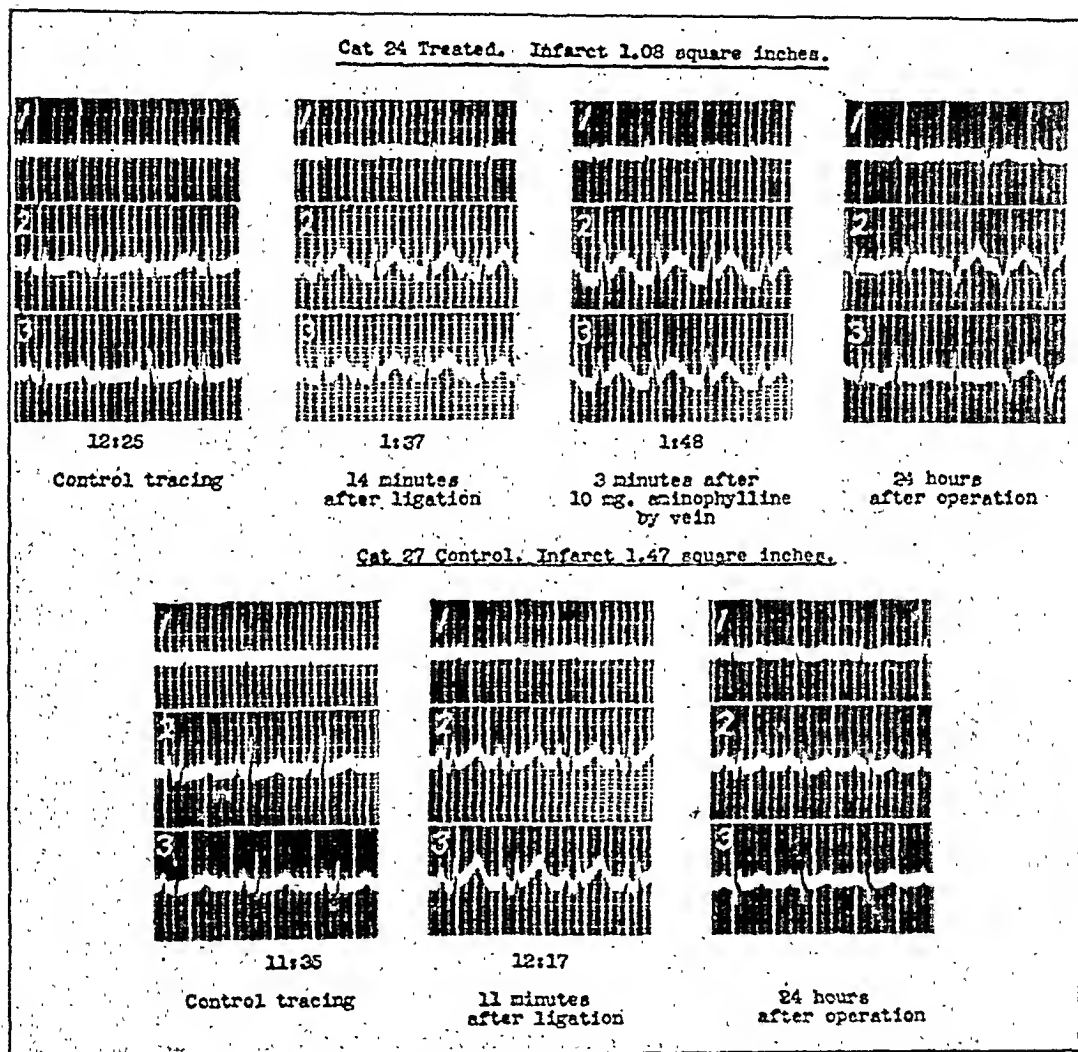


Fig. 4.—Typical electrocardiograms after ligation of circumflex branch of left coronary. Note similar displacement of R-T segment and recovery in twenty-four hours for both control and treated animals, and absence of effect of aminophylline on R-T segment displacement.

two instances, within a few minutes after the ligation did not reduce the displacement of the R-T segment (Fig. 4). Treatment did not shorten the time required for the R-T segment to return to normal, namely, about sixteen days in each group. An observation having a similar significance is the fact that the numbers which failed to show complete return of the segment to the base line at the end of the three-week period

\*Due consideration was given to the fact that in control tracings the R-T segment is sometimes elevated about 0.5 to 1 mm. above the base line.

were equivalent in the two groups. Ventricular tachycardia occurred much more frequently in the treated group (9 of 19 cases, or 47.4 per cent of the treated animals, and 2 of 23 cases, or 8.7 per cent of the controls), although the incidence of this disorder before any treatment was negligible (one in the treated group and two in the controls). This abnormal rhythm appeared in two and eight days respectively, in the control group, and in the other group, during treatment for from two to twenty-one days, averaged six days. This is the second unfavorable factor which has appeared in the treated group. It is apparently not due to the fact that this group had the larger infarcts, for the cases of ventricular tachycardia were dispersed throughout the whole range of size of infarcts, from among the smallest to the largest. This difference may also be purely accidental.

A series of 68 sections from different regions of the hearts, including the center of the infarct, the area of transition and the adjacent musculature, were examined microscopically. Three sections were selected as standards to represent three grades of healing of the infarct:

Slight (large amount of necrotic tissue, relatively few round cells and fibroblasts, and little or no collagen deposition);

Moderate (little or no necrotic tissue, a relatively loose arrangement of round cells and fibroblasts, and an early stage of collagen deposition); and

Advanced (no necrotic tissue whatever, a dense, compact arrangement of round cells and fibroblasts, and an advanced stage of collagen deposition).

With this as a basis of comparison, 29 sections taken from the center of the infarcts were classified independently by each of two of the workers, and without knowledge of their identity as sections from treated or control animals. The results of this comparison show that the microscopic appearance of the infarcts in treated and untreated animals cannot be distinguished (Table II). Photomicrographs of sections showing advanced and slight degrees of healing for typical members of both groups are reproduced in Fig. 5.

#### SUMMARY AND CONCLUSIONS

The present study in cats (19 treated and 23 control) shows that daily treatment with fairly large doses of aminophylline does not exert any influence that can be considered favorable on the course of the infarction resulting from ligation of a large coronary artery, namely, the circumflex branch of the left vessel.

Intensive treatment with this drug for three weeks was without influence on the systemic blood pressure, or on the course of the electrocardiographic changes. Furthermore, it did not accelerate the process of healing, nor did it reduce the size of the infarct.

The results of this study are therefore not in agreement with those which have been reported for the dog. It should be noted that, in addition to factors which have already been indicated, these studies differ with respect to the species of animal and also the vessel ligated. It seems possible that the influence of the collateral circulation after ligation of the entire left circumflex branch may be different from that

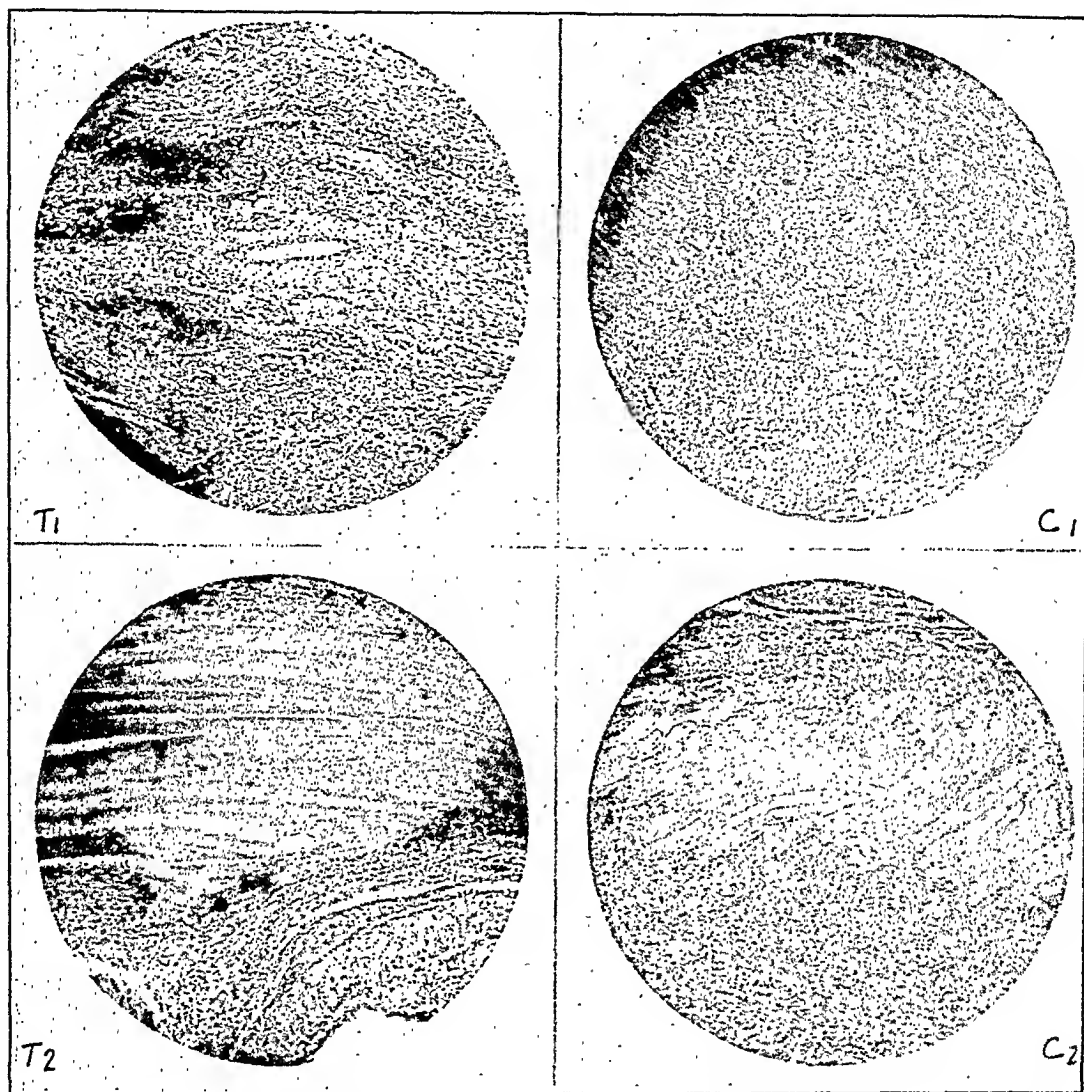


Fig. 5.—Photomicrographs of sections of typical infarcts in both control and treated animals showing advanced and slight degrees of healing in each group at the end of three weeks.

C-1 (control, advanced healing); C-2 (control, slight healing).

T-1 (treated, advanced healing); T-2 (treated, slight healing).

after ligation of a portion of the left descending branch, and that this may in part account for the difference in results obtained.

In any case, the routine use of aminophylline in the treatment of coronary thrombosis receives no support from the results of these experiments. This conclusion is in accord with the results of the recent clinical study by Gold, Kwit, and Otto,<sup>14</sup> which shows that the xanthines are without beneficial influence on the course of pain in angina pectoris.



## REFERENCES

1. Eppinger, H., and Hess, L.: Versuche über die Einwirkung von Arzneimitteln auf überlebende Coronargefäße, *Ztschr. f. exper. Path. u. Therap.* 5: 622, 1909.
2. Gow, D.: Some Reactions of Surviving Arteries, *J. Physiol.* 42: 125, 1911.
3. Heathcote, R. St. A.: The Action of Caffeine, Theobromine and Theophylline on the Mammalian and Batrachian Heart, *J. Pharmacol. & Exper. Therap.* 16: 327, 1920.
4. Guggenheimer, H., and Sassa, K.: Ueber die Beeinflussung des Coronarkreislaufs durch Purinderivate, *Klin. Wehnschr.* 2: 1451, 1923.
5. Fisher, I., Guggenheimer, H., and Müller, E. A.: Ueber die Beeinflussung von Koronardurchblutung und Herztonus durch Theophyllinpräparate und Strophanthin nach Untersuchungen am Starlingsehen Herz-Lungenpräparat, *Deutsche med. Wehnschr.* 54: 1584, 1928.
6. Gilbert, N. C., and Fenn, G. K.: The Effect of the Purine Base Diuretics on the Coronary Flow, *Arch. Int. Med.* 44: 118 (July), 1929.
7. Stoland, O. O., Ginsberg, A. M., Loy, D. L., and Hiebert, P. E.: Studies on Coronary Circulation. IV, *J. Pharmacol. & Exper. Therap.* 51: 387, 1934.
8. Hatcher, R. A., and Kwit, N. T.: The Elimination of Theobromine and Caffeine From the Circulation, *J. Pharmacol. & Exper. Therap.* 52: 430, 1934.
9. Wiggers, C. J., and Greene, H. D.: The Ineffectiveness of Drugs Upon Collateral Flow After Experimental Coronary Occlusion in Dogs, *AM. HEART J.* 11: 527, 1936.
10. Fowler, W. M., Hurevitz, J. M., and Smith, F. M.: Effect of Theophylline Ethylenediamine on Experimentally Induced Cardiac Infarction in the Dog, *Arch. Int. Med.* 56: 1242, 1935.
11. Smith, F. M., Rathe, H. W., and Paul, W. D.: Theophyllin in the Treatment of Disease of the Coronary Arteries, *Arch. Int. Med.* 56: 1250, 1935.
12. Travell, J., Gold, H., and Modell, W.: The Effect of Myocardial Infarction on the Tolerance to Digitalis, in press.
13. Gold, H., Hitzig, W., Gelfand, B., and Glassman, H.: A Qualitative Comparison of Various Digitalis Bodies, *AM. HEART J.* 6: 237 (Dec.), 1930.
14. Gold, H., Kwit, N., and Otto, H.: The Xanthines (Theobromine and Aminophylline) in the Treatment of Cardiac Pain, *J. A. M. A.* 108: 2. 173. 1937.

# THE SIGNIFICANCE OF AN ABSENT OR A SMALL INITIAL POSITIVE DEFLECTION IN THE PRECORDIAL LEAD\*

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## INTRODUCTION

IN RECENT years the value of the preecordial lead as an aid in the diagnosis of myocardial damage, and particularly of infarction, has been well established. The significance of absence of the initial positive deflection or Q-wave has been emphasized in many of the reports dealing with the precordial lead. In hundreds of normal controls cited in the literature<sup>1-15</sup> this wave has never been absent and as a rule has measured more than 2 mm., although occasionally a deflection as small as 1 mm. has been noted. On the other hand Wolferth and Wilson and their coworkers<sup>16-21</sup> have found the initial positive deflection frequently absent in coronary occlusion, clinical and experimental, with infarction of the anterior surface of the heart. This did not hold for posterior infarction. Wood et al.<sup>3</sup> later reported that it was rarely absent in other conditions, such as bundle-branch block and advanced myocardial disease without coronary occlusion. Bohning and Katz<sup>11</sup> found a small initial positive deflection frequently in coronary sclerosis. Recently, Levine and Levine<sup>22</sup> have reviewed the precordial lead in coronary disease with particular attention to the initial positive deflection. Their post-mortem observations showed that not only was absence of this deflection nearly always associated with myocardial infarction but also that infarction was present in one-half of the patients with an initial positive deflection measuring 2 mm. or less. They concluded, therefore, that the absence of this deflection was indicative of myocardial infarction and assumed this to be present in patients with angina pectoris even when there was no history of coronary thrombosis. Moreover, these authors almost always encountered an absent or small initial positive deflection in bundle-branch block in the absence of myocardial infarction.<sup>23</sup> In a series of cases of coronary occlusion analyzed by Jervell<sup>20</sup> the initial positive deflection was absent only when there was recent or old infarction of the anterior surface of the left ventricle.

## METHOD AND DATA

At the Mount Sinai Hospital the precordial lead has been taken routinely in addition to the standard leads since 1934. Our interest

\*From the Cardiographic Laboratory, Mount Sinai Hospital.

This study was assisted by funds donated by Mr. Frank Altschul, Mrs. Charles Altschul, and Mr. Herbert H. Lehman.

in the significance of the initial positive deflection in the precordial lead was aroused early by finding it absent or small in several cases without myocardial damage or with damage not associated with coronary artery disease. Furthermore, the relative significance of an absent and a small initial positive deflection was uncertain. We have therefore analyzed the electrocardiograms obtained in 4,500 consecutive patients between April, 1934, and October, 1936, with particular attention to the initial positive deflection.

The chest lead was taken by the method previously described by us.<sup>9, 15</sup> The right arm electrode was placed over the precordium just within the apex, in the fourth or fifth interspace, and the left leg served as the site of the indifferent electrode. By this method positivity of the precordial electrode is represented by a wave directed downward, and negativity by a wave directed upward, the opposite of that which obtains in the standard leads. The precordial electro-

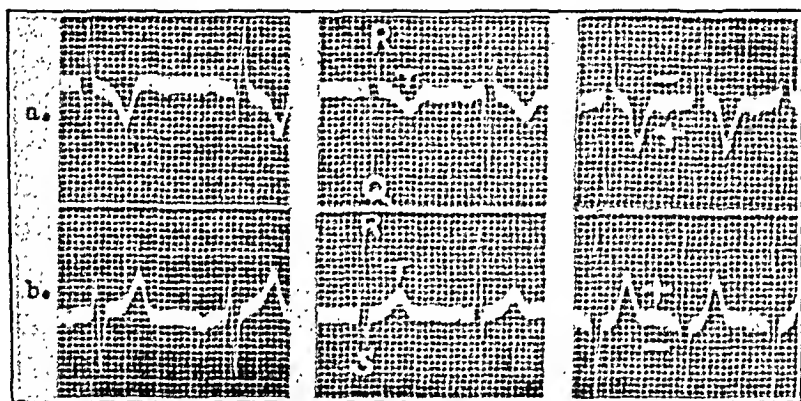


Fig. 1.—Three examples of normal precordial lead. (a) Recorded in the customary manner so that negativity of the precordial electrode is represented by an upward deflection. The old nomenclature is given—an initial downstroke Q, followed by the intrinsic deflection R. In the third example there is a small initial upward deflection preceding the Q. The T-wave is inverted. (b) Recorded so that negativity of the precordial electrode is represented by a downward deflection. New nomenclature—an initial upward deflection R, and an intrinsic deflection S. In example three there is a small Q. The T-wave is upright.

cardiogram thus obtained (Fig. 1a) consists of an initial downward positive deflection (Q-wave) followed by an upward negative deflection (R-wave); the T-wave is inverted. Since the introduction of the precordial lead into routine use, it has been suggested by some<sup>6, 10, 12, 13, 24, 29</sup> including the senior author,<sup>9</sup> that the polarity of the circuit be reversed so that the direction of the waves would conform to that in the standard leads. This is accomplished by attaching the left leg lead wire to the precordial electrode and the right arm lead wire to the indifferent electrode. The QRS complex then consists of an initial positive upward deflection, the R-wave, followed by a negative downward intrinsic deflection, the S-wave and the T-wave is upright (Fig. 1b). Not infrequently a small negative deflection precedes the R-wave which is called Q-wave. Recently, Wilson<sup>21</sup> maintained that this arrangement

is theoretically more correct and has advocated the change. It is our belief that it will be adopted by other workers in the near future. In order to avoid confusion until this is done, in this paper the components of the QRS group will be referred to respectively as the initial positive deflection (Q-wave of old technique, R-wave of new) and the intrinsic negative deflection (R-wave of old technique, S-wave of new).

In 64 patients the precordial lead was also studied with the precordial electrode placed at five different positions on the chest wall. Position 1 was two cm. to the right of the right sternal line in the fourth interspace; position 2 was in the midsternal line; position 3 was two cm. to the left of the left sternal line in the fifth interspace; position 4, just within the cardiac apex; position 5, outside the apex. In these 64 patients, furthermore, the "neutral point" or "zero potential" method, advocated by Wilson et al.<sup>19</sup> and Kossman and Johnston,<sup>13</sup> was employed to determine if it possessed any practical advantage over the ordinary procedure described above. The comparative results obtained will be discussed later.

#### ANALYSIS OF CASES WITH ABSENT INITIAL POSITIVE DEFLECTIONS

The initial positive deflection was absent in 120 (2.7 per cent) of the 4,500 consecutive patients in whom precordial leads were taken. Seventy-nine of these (66 per cent) were known to have sustained a coronary occlusion, recent or old; in the remainder (34 per cent) no such history could be elicited nor did the clinical course suggest the presence of coronary occlusion. A perusal of Table I shows that in all but two of the cases of coronary occlusion there was infarction of the anterior wall of the heart or a combination of anterior and posterior wall infarction (Figs. 2, 3). Two cases were considered to present infarction of the posterior wall alone, since each presented the typical electrocardiographic pattern ( $Q_2$ ,  $T_2$ ;  $Q_3$ ,  $T_3$ ) (Figs. 4, 15) and in one, post-mortem examination revealed thrombosis of the right coronary artery with posterior infarction. However, in this case there was also an old partial occlusion of the left anterior descending artery. While no evidence of infarction was found on the anterior wall it is possible that it had formerly been present, which might explain the absence of the initial positive deflection. Thus when the initial positive deflection of the precordial lead was absent in coronary thrombosis, the standard leads nearly always showed a  $Q_1$ ,  $T_1$  pattern and necropsy revealed infarction of the anterior surface of the heart.

In the group of 41 patients with an absent initial positive deflection but without a definite clinical history of coronary thrombosis, 27 exhibited unequivocal clinical or electrocardiographic evidence of myocardial damage associated with arteriosclerotic heart disease or long-standing hypertension. Only three of these patients came to

post-mortem examination but all showed recent or old coronary occlusion with anterior or both anterior and posterior wall infarction. Although many of the remaining 24 patients had never had precordial pain, and those with angina pectoris had never had a major attack which could be interpreted as a coronary occlusion, a previous silent or gradual coronary closure could not be definitely ruled out in view of the marked cardiac damage present in these cases and of the post-mortem findings in the above three cases. In these 24 patients, there-

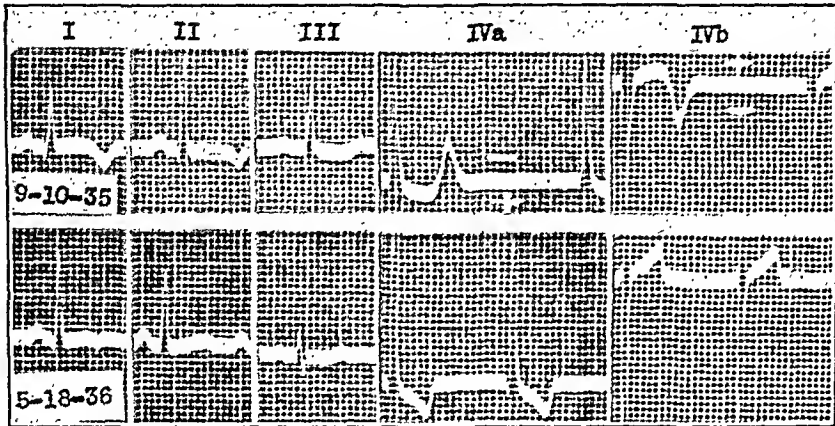


Fig. 2.—Acute coronary thrombosis (anterior wall infarction). Male, aged forty years. Sept. 10, 1935. One week after the attack. The standard leads show cove-plane  $T_1$  and  $T_2$ . In the precordial lead the T-wave is directed oppositely to the normal and the initial positive deflection is absent. This is the typical appearance in anterior wall infarction. May 18, 1936. The standard leads are returning to normal although  $T_1$  still is semi-inverted.  $T_4$  has become normal. The initial positive deflection has reappeared but is small. This small deflection may be the only remaining abnormality following coronary occlusion.

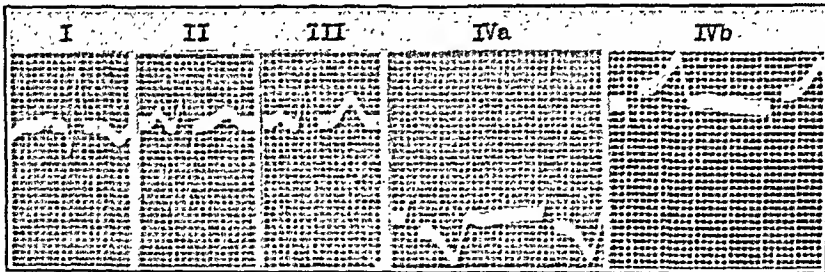


Fig. 3.—Old coronary thrombosis. Male, aged sixty years. Post-mortem examination shows an old occlusion of the left anterior descending coronary artery with an aneurism of the left ventricle. The standard leads show marked LVP, large  $Q_1$  and inverted  $T_1$ , characteristic of anterior wall infarction. The only abnormality in the precordial lead is absence of the initial positive deflection.

fore, it is possible that the absence of the initial positive deflection represented unrecognized myocardial infarction, as Levine and Levine<sup>22</sup> believed to be the case in their patients with angina pectoris. On the other hand, we have seen this finding present in patients with advanced coronary sclerosis,<sup>3</sup> bundle-branch or intraventricular block<sup>3, 22, 23</sup> or only an enlarged left ventricle<sup>25</sup> in the absence of coronary thrombosis. It may be that the absence of the initial posi-

tive deflection in our group can be explained in this way, for the majority had marked enlargement of the heart as a result of long-standing hypertension and the standard lead electrocardiogram often showed a typical hypertensive pattern, that is, marked left ventricular preponderance, high voltage and  $T_1$  inversion (Fig. 5). Still others showed marked intraventricular conduction defects and occasionally bundle-branch block (Fig. 6). Additional post-mortem examinations are necessary to settle this point.

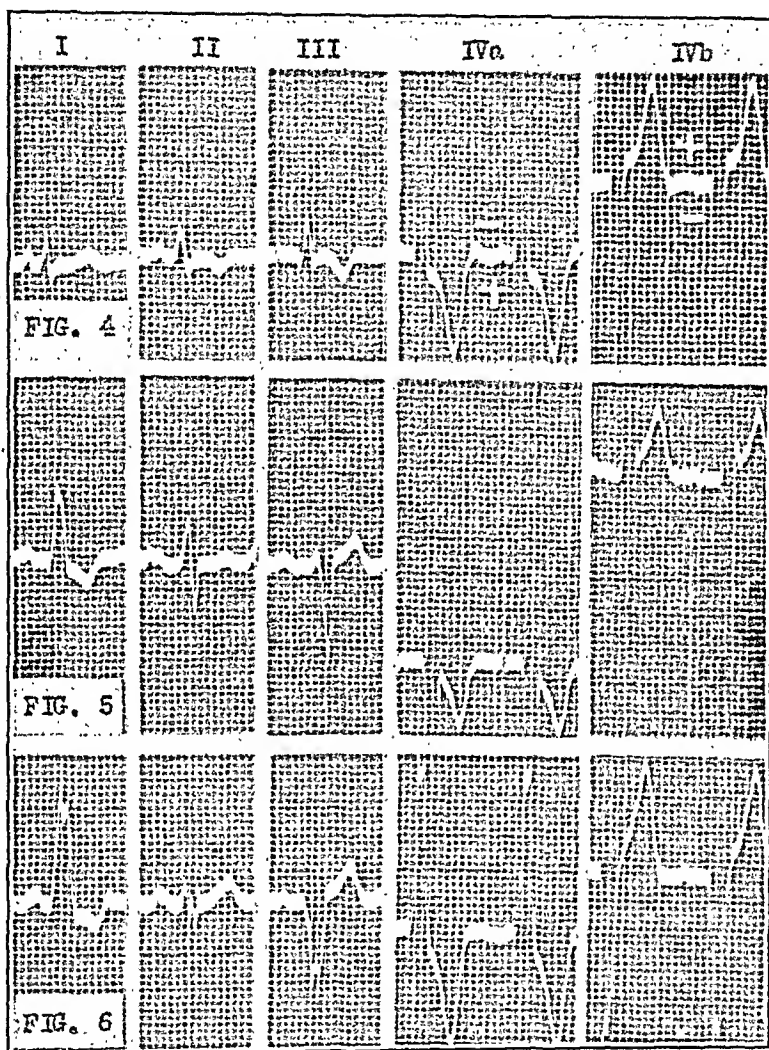


Fig. 4.—Recent coronary thrombosis. Male, aged sixty-two years. Standard leads show  $T_2$   $T_3$  pattern characteristic of a posterior wall infarction. The precordial lead shows almost complete disappearance of the initial positive deflection. The T-wave is of high amplitude but of normal direction.

Fig. 5.—Calcific aortic stenosis. Male, aged fifty-five years. At post-mortem examination the left ventricle was enormously hypertrophied and the heart weighed 1,050 gm., but the coronary arteries were normal. The standard leads are characteristic of enlargement of the left ventricle. The initial positive deflection in the precordial lead is extremely small. Note the huge negative intrinsic deflection. The  $T_1$  is normal.

Fig. 6.—Essential hypertension. Female, aged fifty-two years. No history or clinical evidence of previous coronary occlusion. Left bundle-branch block with a small to absent initial positive deflection in the precordial lead.

#### *Absent Initial Positive Deflection in Cases Without Infarction.—*

There remain 14 patients with absence of the initial positive deflection in which the diagnoses were miscellaneous (Table I). The presence of

myocardial infarction in this group was most improbable, because of the comparative youth of the patients as well as the clinical course. These cases were diagnosed acute or chronic nephritis, 4; rheumatic cardiovalvular disease, 3; syphilitic heart disease, 2; spontaneous pneumothorax, 2; acute myocarditis of unknown etiology, 1; thyrotoxic heart disease, 1; and severe anemia, 1. The patients with acute nephritis were aged fifteen, twenty-seven, and forty years respectively. There was no clinical evidence of coronary disease although definite electrocardiographic changes were present (Figs. 7, 8). The latter are common during the course of acute glomerulonephritis and have

TABLE I  
ANALYSIS OF 120 CASES OF ABSENT INITIAL POSITIVE DEFLECTION

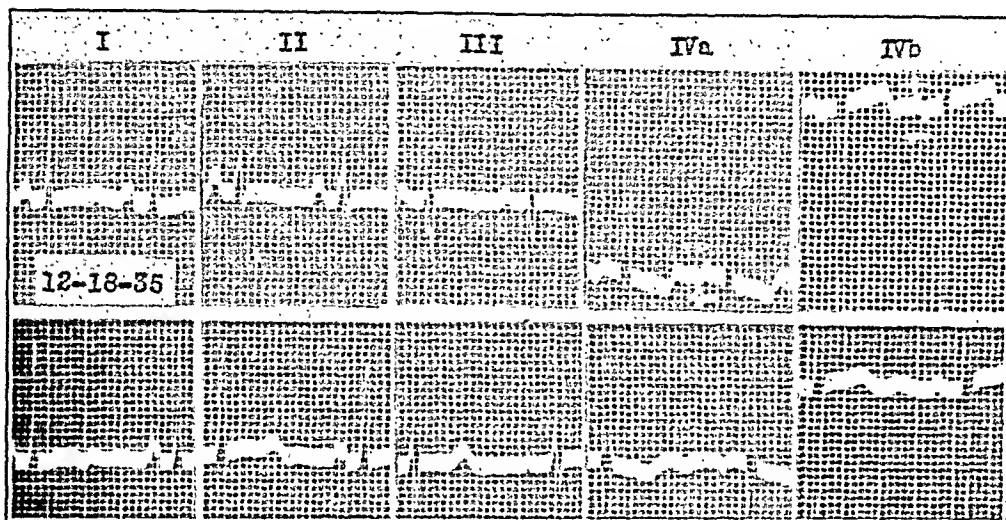
| CLINICAL DIAGNOSIS (120 CASES)                         | POST-MORTEM (15 CASES)   |
|--|--|
| 79 old or recent coronary occlusion                    | 12 old or recent myocardial infarction   |
| 69 anterior ( $Q_1$ $T_1$ type)                        | 8 anterior wall infarction with LAD occlusion  |
| 2 posterior ( $Q_2$ $T_2$ type)                        | 1 posterior wall infarction with right coronary and old partial LAD occlusion        |
| 8 anterior and posterior                               | 3 anterior and posterior wall infarction with LAD and right coronary occlusion       |
| 41 no history or clinical signs of coronary thrombosis |  |
| 27 arteriosclerotic or hypertensive heart disease      | 3 old or recent coronary thrombosis with anterior wall infarction with LAD occlusion |
| 14 miscellaneous diagnoses                             |  |
| 3 rheumatic cardiovalvular disease                     |  |
| 2 cardiovascular syphilis                              |  |
| 3 acute nephritis                                      |  |
| 1 chronic nephritis                                    |  |
| 1 acute myocarditis, unknown etiology                  |  |
| 2 spontaneous pneumothorax                             |  |
| 1 thyrotoxic heart disease                             |  |
| 1 severe anemia  |  |

already been reported by us.<sup>26</sup> These changes are transient, including absence of the initial positive deflection, and may be explained on the basis of myocardial involvement as a result of diffuse capillary damage which occurs in acute glomerulonephritis.

In two instances of spontaneous pneumothorax the initial positive deflection was absent and in two others it was very small. In all four there was definite displacement of the mediastinum as seen on roentgenogram and the standard lead electrocardiogram revealed a peculiar axis deviation apparently due to rotation of the heart (Fig. 9). In three cases, absorption of the pneumothorax, with re-expansion of the collapsed lung and return of the mediastinum to its usual position, was accompanied by a return to normal of the electrical axis and of



the initial positive deflection. It is thus evident that rotation or displacement of the mediastinum, in the absence of cardiac disease, may not only distort the electrical axis in the standard leads, as already demonstrated by one of us,<sup>28</sup> but may also cause disappearance or marked diminution in size of the initial positive deflection of the precordial lead.



(1-8-36)

Fig. 7.—Acute glomerulonephritis. Male, aged twenty-seven years. Dec. 18, 1935. Flat T-waves in standard leads. In the precordial lead the initial positive deflection is absent and the T-wave is diphasic. Jan. 8, 1936. T<sub>1</sub> has become inverted, T<sub>2</sub> and T<sub>3</sub> are normal. The initial positive deflection has reappeared and T<sub>4</sub> is normal.

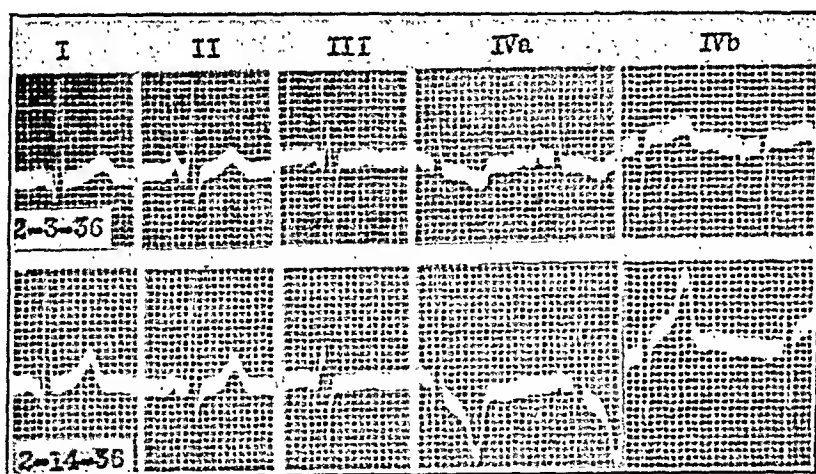


Fig. 8.—Acute glomerulonephritis. Male, aged sixteen years. Feb. 3, 1936. Standard leads normal except for LVP. The only definite abnormality present is absence of the initial positive deflection in the precordial lead. Feb. 14, 1936. Standard leads are unchanged. The initial positive deflection of the precordial lead has reappeared and T<sub>4</sub> is of higher amplitude.

Three other patients in this miscellaneous group were males, aged thirty-five, thirty-six, and thirty-nine years respectively, who suffered from chronic rheumatic valvular disease. Two of these had aortic insufficiency with marked left ventricular preponderance and a large left ventricle (Figs. 10 and 12) and one had mitral stenosis with right ventricular preponderance and a large right ventricle (Fig. 11). These three



cases emphasize again that a large heart may lead to disappearance of the initial positive deflection in the absence of myocardial infarction.

*Summary.*—It is seen that absence of the initial positive deflection in the precordial lead nearly always signifies myocardial involvement. In two-thirds of the cases of this series it was due to myocardial infarction involving the anterior surface of the heart, very rarely the posterior wall. It may be absent also in patients with conditions other than myocardial infarction or coronary sclerosis, such as glomerulonephritis,

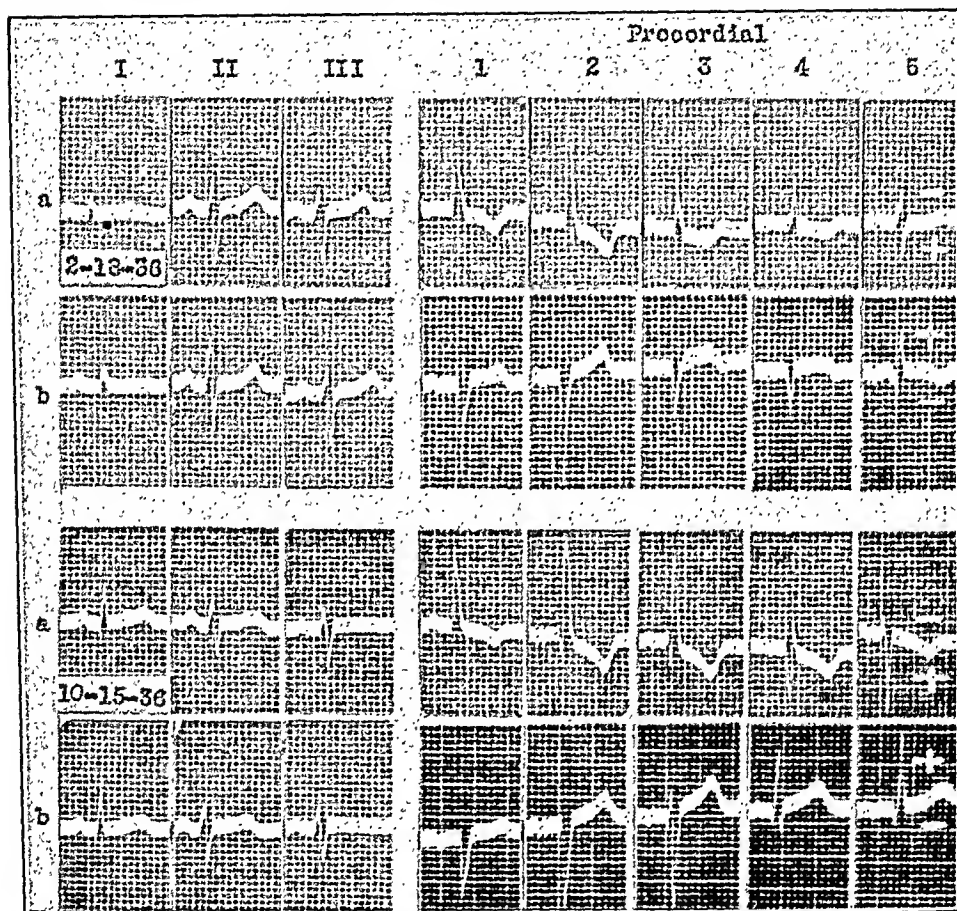


Fig. 9.—Tension pneumothorax, left side. Male, aged twenty-one years. Feb. 18, 1936. The standard leads show an unusual electrical axis due to rotation and displacement of the heart. The precordial lead shows absence of the initial positive deflection in all positions on the chest wall. The T-wave is diphasic in positions 3, 4, and 5. Oct. 15, 1936. Almost complete absorption of the pneumothorax. The heart has returned to the normal position. There is now left axis deviation. The initial positive deflection has reappeared in all positions except position 1. The T-wave is normal.

(Position 1 is two cm. to the right of the right sternal line. Position 2 is at the midsternum. Position 3 is two cm. to the left of the left sternal line. Position 4 is just within the apex. Position 5 is outside the apex.)

rheumatic and syphilitic heart disease, intraventricular block. Finally, rotation or displacement of an otherwise normal heart may produce disappearance of the initial positive deflection.

*QRS of Unusual Form (M and W-shaped QRS).*—In 24 patients included in the group with an absent initial positive deflection the QRS

complex of the precordial lead was of an unusual form (Figs. 13, 14, 15). This type of QRS group was often widened and consisted of a large initial negative wave followed by a more or less large positive wave and frequently a second negative wave (W or M type). Bohning and Katz<sup>11</sup> pointed out the frequency of such a QRS group in patients with coronary sclerosis or intraventricular block. In the majority of cases we found this type of ventricular complex to have the same significance as that in which the initial positive wave was absent and only a large negative wave present. In recording the precordial lead in these patients in the five positions on the chest wall described pre-

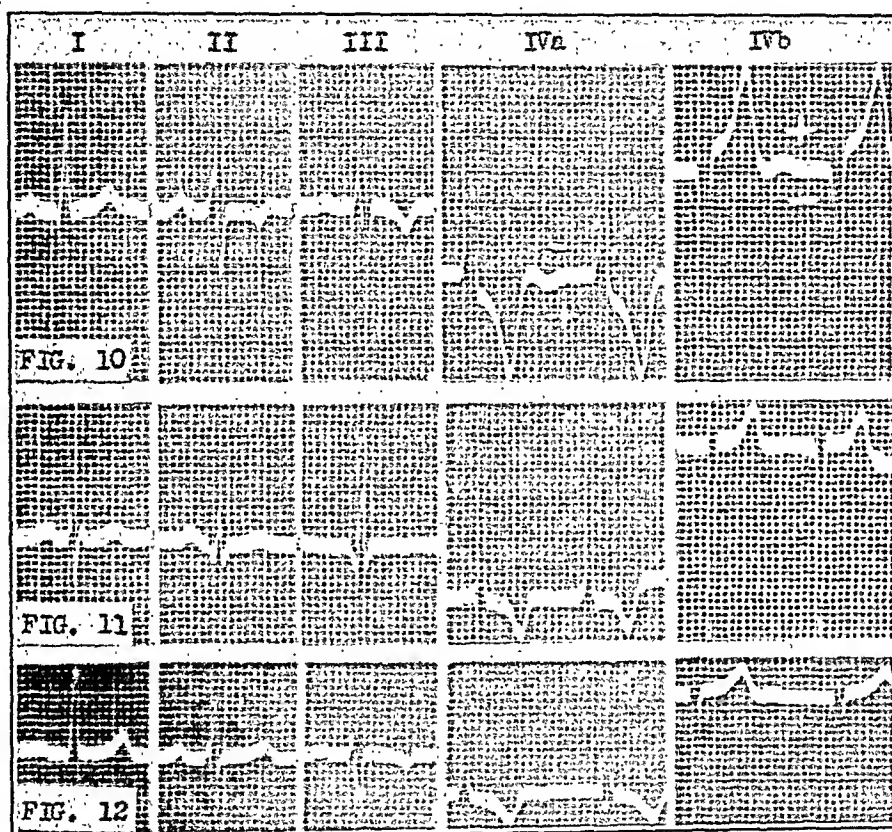


Fig. 10.—Chronic rheumatic valvular disease, aortic insufficiency. Male, aged thirty-six years. Left ventricle markedly enlarged. Standard leads show marked LVP and inversion of  $T_2$  and  $T_3$ . The initial positive deflection in the precordial lead is absent and the  $T_4$  is of high amplitude.

Fig. 11.—Chronic rheumatic valvular disease, mitral stenosis. Male, aged thirty-seven years. Enlarged left auricle and right ventricle. The standard leads show marked RVP. The initial positive deflection in the precordial lead varies from small to absent. The  $T_4$  is normal.

Fig. 12.—Chronic rheumatic valvular disease, mitral stenosis, and aortic insufficiency. Male aged twenty-one years. Standard leads show only LVP and  $T_3$  inversion. The initial positive deflection is extremely small. The  $T_4$  is normal.

viously, it was noted that when an M or W-shaped QRS was present in the routine position (just within the apex), the ordinary type of complex with an absent initial positive deflection frequently appeared in the other positions on the chest wall (Figs. 13, 14, 15). Thus when an abnormal QRS of this type is observed in the routine precordial lead, one should repeat the electrocardiogram obtaining records from

the various positions across the chest. This procedure will usually demonstrate an absent initial deflection in one or more of these positions. Occasionally there was observed a transition from an M-shaped QRS to a monophasic QRS in the same record, probably due to different phases of respiration (Fig. 16). All the patients presenting this abnormal type of QRS had marked myocardial disease and 15 of the 24 had suffered a coronary occlusion. Wilson and his coworkers<sup>20, 21</sup> have suggested that an M or W-shaped QRS group appears when only the inner layers of the ventricular wall are infarcted or when the precordial electrode is placed over the edge of an area of infarction.

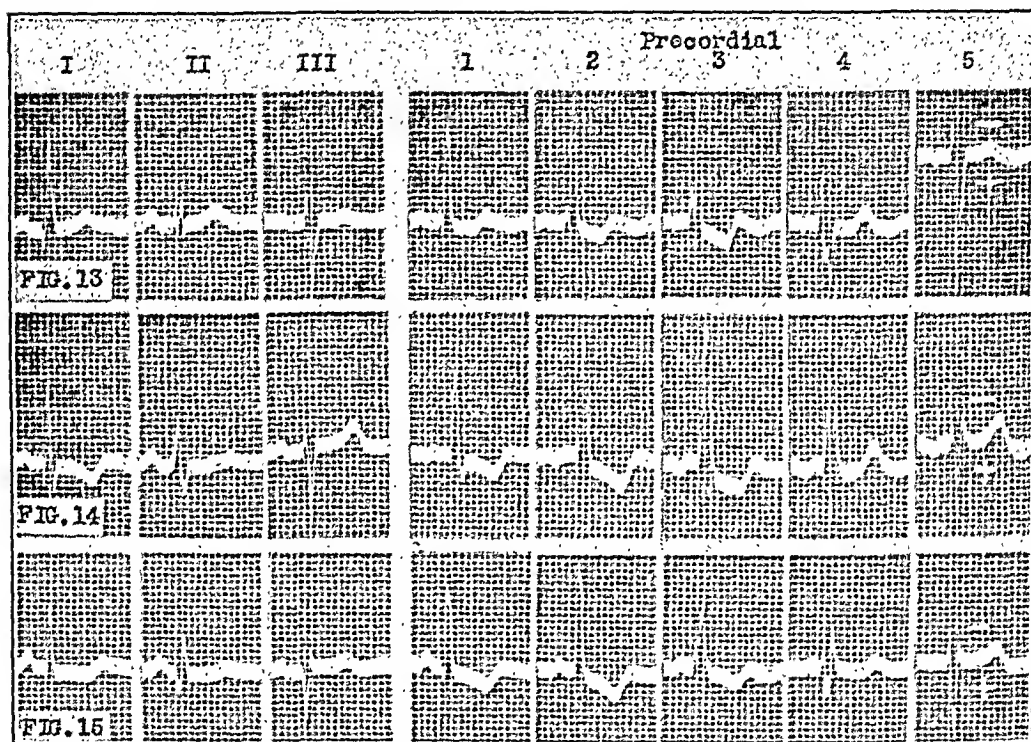


Fig. 13.—Coronary thrombosis two years previously (anterior wall infarction). Male, aged forty-nine years. Standard leads present residual  $Q_1$  and W-shaped QRS in Lead II. The QRS complex in the routine precordial lead (position 4) is of an abnormal type (R-S type) and the T-wave is directed opposite to the normal. Other positions (1, 2, 3) show absence of the initial positive deflection.

Fig. 14.—Coronary thrombosis two years previously (anterior wall infarction). Male, aged fifty-nine years. Standard leads show  $Q_1$   $T_1$  pattern. The QRS in the routine precordial lead (position 4) is M-shaped and the T-wave is opposite to the normal. In positions 1, 2, and 3 the initial positive deflection is absent.

Fig. 15.—Coronary thrombosis two years previously (posterior wall infarction). Male, aged forty-nine years. Standard leads show  $Q_2$   $Q_2$  pattern. Routine precordial lead (position 4) shows M-shaped QRS and an abnormal T-wave. The initial positive deflection is absent in positions 2 and 3.

When the electrode is moved toward the center of the infarct the QRS will become of the usual type with a single negative deflection.

*Permanence of Absence of the Initial Positive Deflection.*—Eighty-three patients with an absent initial positive deflection had repeated electrocardiograms; in 14 of these the positive deflection reappeared.

This group comprised 11 patients suffering from recent coronary thrombosis (Figs. 2, 18, 19), two from acute nephritis (Figs. 7, 8) and one from spontaneous pneumothorax (Fig. 9). In four of the patients with coronary thrombosis the deflection which reappeared remained small (Fig. 2). The time of reappearance varied considerably, the shortest interval being three days and the longest, one year. However, these figures are not precise since the electrocardiograms were not always taken at regular intervals. The reappearance of this deflection was not always associated with changes in the standard leads.

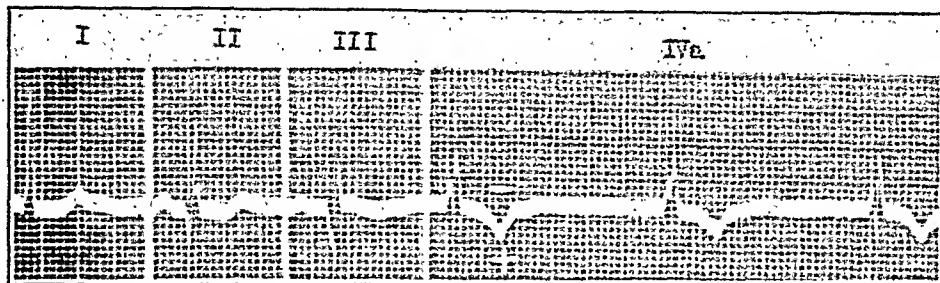


Fig. 16.—Old coronary thrombosis two years previously (posterior wall infarction). Male, aged sixty years. Standard leads show Q: Q: T: pattern. The precordial lead shows an abnormal M-shaped QRS which varies in appearance from beat to beat. In the second beat the initial positive deflection is seen to be absent.

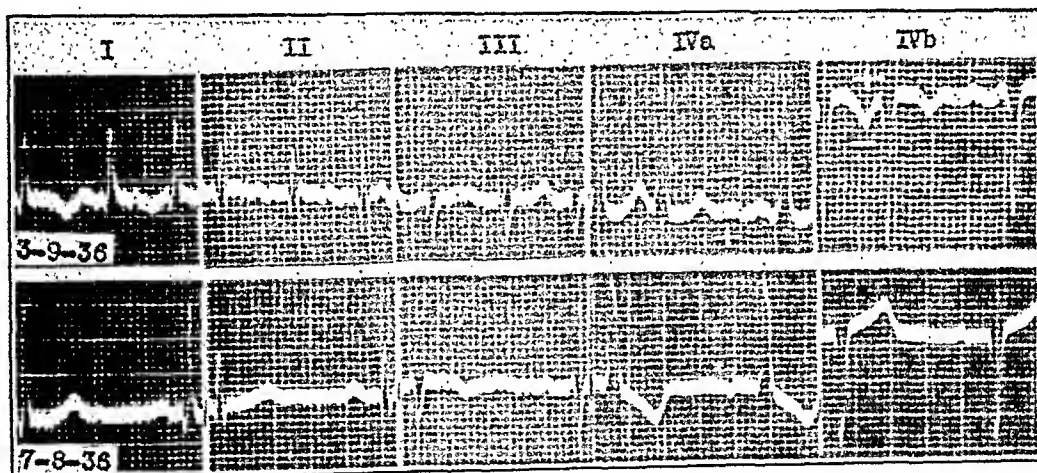


Fig. 17.—Recent coronary thrombosis (anterior wall infarction). Female, aged fifty years. Mar. 9, 1936. Three weeks after acute attack. Standard leads show auricular fibrillation, small Q<sub>i</sub> and inversion of T<sub>i</sub>. In the precordial lead which is characteristic of anterior infarction the initial positive deflection is absent and the T-wave is directed opposite to the normal. July 8, 1936. Four months later. The standard leads have returned to normal except for the small Q<sub>i</sub>. The T<sub>i</sub> has also become normal but the initial downward deflection is still absent. This is the only remaining sign of previous infarction.

for in several cases the latter remained abnormal (Figs. 18, 19). Nor did this wave reappear in every case in which definite clinical improvement occurred. In many of the cases of coronary thrombosis observed since 1934, it has remained absent until the present time despite disappearance of clinical symptoms and of many of the abnormalities in the standard leads (Figs. 13, 17). Similar observations were reported by Wood and his associates.<sup>3</sup>

*Correlation of Absent Initial Positive Deflection With Abnormal T-wave.*—In somewhat over half the cases an absent initial positive deflection was accompanied by an abnormal T-wave, that is, one of negative polarity (upright T-wave of old terminology) (Figs. 2, 17). Nearly all these (82 per cent) were cases of coronary thrombosis. The presence of both of these abnormalities is therefore characteristic of

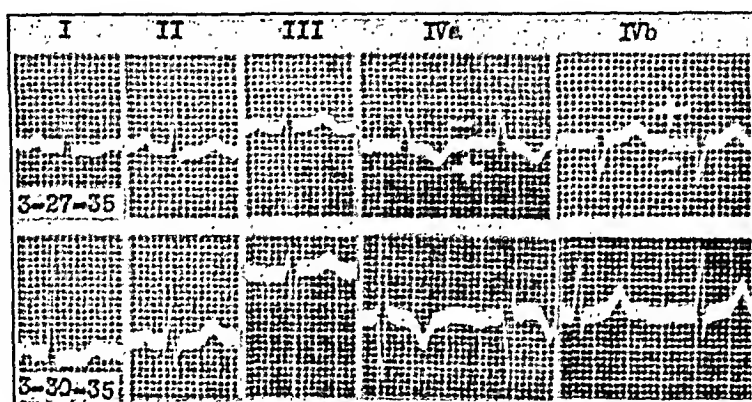


Fig. 18.—Acute coronary thrombosis. Female, aged fifty-nine years. Mar. 27, 1935. Three days after the acute attack. Standard leads show LVP and biphasic T<sub>1</sub>. The initial positive deflection is very small. T<sub>1</sub> is normal. Mar. 30, 1935. No change in the standard leads. The initial positive deflection has returned to normal within three days.

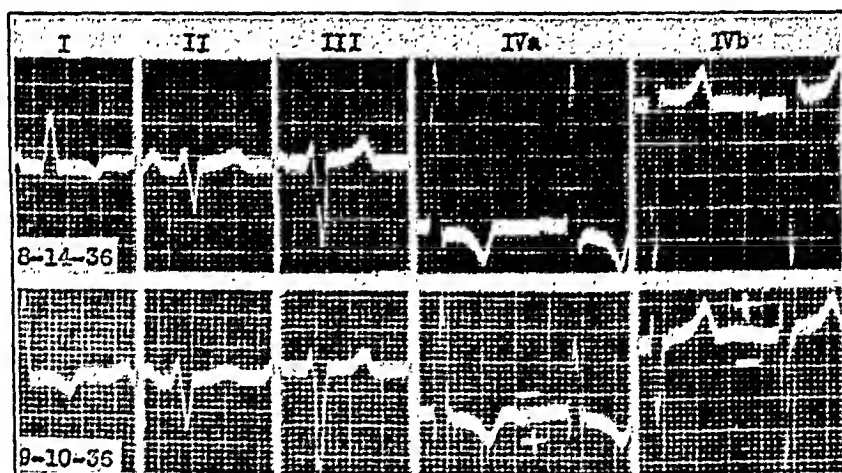


Fig. 19.—Acute coronary thrombosis (anterior wall infarction). Male, aged forty-eight years. Aug. 14, 1936. One week after the acute attack. The standard leads show marked LVP. Intraventricular conduction defect and T<sub>1</sub> inversion. The initial positive deflection of the precordial lead is absent but T<sub>1</sub> is normal. Sept. 10, 1936. No change in the standard leads. The initial positive deflection has reappeared within one month.

anterior wall infarction. On the other hand 46 per cent of cases with absent initial positive deflection presented a normal T-wave, that is, one of positive polarity; while myocardial involvement was present in all of these, only nine had infarction (Figs. 3, 19). In the latter cases the absent initial positive deflection was the only sign in the precordial lead of infarction. Occasionally there was very little abnormality



even in the standard leads, particularly following recovery from an attack of thrombosis (Fig. 17). Moreover in several cases of recent coronary thrombosis the initial deflection remained absent or small long after an abnormal R-T transition or T-wave had returned to normal (Figs. 2, 17). As Wilson et al.<sup>17</sup> have already pointed out, the QRS changes following myocardial infarction are more permanent than the T-wave changes. Our own observations corroborate this, for only in a small percentage of cases did the initial positive deflection reappear after one to two years.

#### ANALYSIS OF CASES WITH SMALL INITIAL POSITIVE DEFLECTION

In addition to absence of the initial positive deflection a study was made of those cases in which, while present, it measured only 2 mm. or less. One hundred and seventy-five or 3.9 per cent of the 4,500 patients studied showed this finding. Nearly all these patients (92.5 per cent) had definite clinical or electrocardiographic evidences of myocardial involvement. In only 13 patients (7.5 per cent) was the heart presumably normal.

Eighty-four per cent of the patients with a small initial deflection showed abnormalities in the three standard leads indicative of myocardial damage. Bundle-branch block occurred in 11 per cent and a definitely enlarged heart in over one-half of the cases. Analysis of the clinical and pathological diagnoses in the 175 cases revealed the following (Table II): 51 (29 per cent) had recent or old coronary thrombosis (Figs. 2, 18); 65 (37 per cent) had coronary artery disease with or without hypertension; 25 (14 per cent) had chronic rheumatic valvular disease (Figs. 5, 11, 12). The remaining 21 cases included essential hypertension, chronic pulmonary disease, subacute bacterial endocarditis, acute and chronic nephritis, syphilitic aortitis, thyroid heart disease, paroxysmal tachycardia, and Libman-Sacks' disease. The 13 patients (7.5 per cent) without any clinical or electrocardiographic signs of cardiac involvement were admitted with the following diagnoses: mild essential hypertension, spontaneous pneumothorax, obesity, hypoplastic heart, thyroiditis, myasthenia gravis, infectious arthritis, and psychoneurosis.

It is thus seen that an initial positive deflection in the precordial lead measuring 2 mm. or less is almost always definitely abnormal and in the vast majority of instances is observed in patients with myocardial involvement, usually associated with coronary sclerosis with or without thrombosis. A small initial deflection may be the only abnormality found in the precordial lead, even when the standard leads present definite abnormalities, including T-wave changes (Figs. 2, 5, 11, 12, 18). Thus in only 35 cases (20 per cent) was the small initial positive deflection accompanied by an abnormal T-wave in the pre-

eordial lead. This is in contrast with an incidence of 54 per cent in patients with an absent deflection. Similarly, the incidence of coronary thrombosis in the former group was smaller, that is, only 40 per cent. Yet, it is our feeling that in the cases of coronary thrombosis the small initial positive deflection was just as significant as the abnormal T-wave. The importance of a small initial positive deflection

TABLE II

## ANALYSIS OF 175 CASES WITH SMALL INITIAL POSITIVE DEFLECTION

| CLINICAL DIAGNOSIS (175 CASES)                              | POST-MORTEM (26 CASES)   |
|---|--|
| 50 recent or old coronary thrombosis-----                   | 14 recent or old coronary thrombosis<br>2 anterior wall infarction<br>4 posterior wall infarction<br>8 anterior and posterior infarction |
| 66 arteriosclerotic or hypertensive-----<br>heart disease   | 1 recent and old coronary thrombosis<br>(posterior infarction)<br>6 coronary sclerosis   |
| 25 rheumatic valvular disease-----                          | 2 rheumatic valvular disease (mitral<br>and aortic)  |
| 7 chronic pulmonary disease                                 |  |
| 3 essential hypertension with abnormal<br>electrocardiogram |  |
| 6 miscellaneous heart disease                               |  |
| 2 subacute bacterial endocarditis-----                      | 1 subacute bacterial endocarditis in<br>syphilitic aortic insufficiency  |
| 1 Libman-Sacks' disease-----                                | 1 atypical verrucous endocarditis with<br>myocarditis  |
| 1 syphilitic aortitis                                       |  |
| 2 paroxysmal tachycardia                                    |  |
| 5 miscellaneous disease                                     |  |
| 1 chronic nephritis   |  |
| 2 acute nephritis   |  |
| 1 colloid goiter  |  |
| 1 myxedema  |  |
| 13 no heart disease   |  |
| 2 obesity -----   | 1 flabby heart but normal myocardium   |
| 4 essential hypertension with normal<br>hearts              |  |
| 2 spontaneous pneumothorax                                  |  |
| 1 hypoplastic heart   |  |
| 1 thyroiditis   |  |
| 1 myasthenia gravis   |  |
| 1 infectious arthritis                                      |  |
| 1 psychoneurosis  |  |

is further emphasized by the observation that it may frequently disappear entirely for several beats and then reappear (Figs. 8, 11). As this was usually a phasic change it was probably dependent on the respiratory movements of the heart. Furthermore, a small deflection not infrequently disappeared when the precordial electrode was shifted a few centimeters on the chest wall. Thus a sharp separation of absent or very small initial positive deflections was not always possible.

Very little importance has been attached to the height of the intrinsic negative deflection\* in the precordial lead since it may vary so

\*Upward R-wave of old technique, downward S-wave of new.

much in normal records; it may be very large or very small (Fig. 1). However, some useful information may be gathered from correlation of the amplitude of the two deflections of the QRS. It was found that nearly all the patients with a small initial positive deflection and no evidence of heart disease had an intrinsic deflection measuring not more than 10 mm. The patients with coronary thrombosis usually had a large intrinsic deflection in the presence of a small initial deflection. Thus the significance of the latter is greater when the amplitude of the succeeding deflection is above 10 mm. For example, an initial positive deflection of 1.5 mm. appears less significant to us when the intrinsic negative deflection is 7 mm. than when it is 17 mm. Again, an initial positive deflection of 2 mm. with an intrinsic deflection less than 10 mm. is equivocal, but if the latter is 20 mm. or more we are certain that such an initial positive deflection is abnormal. Hence in doubtful cases it is wise to correlate the amplitude of the two deflections of the QRS group.

#### VARIATION IN SIZE OF THE INITIAL POSITIVE DEFLECTION

It is well known that the QRS complex in the precordial lead shows variations in amplitude in repeated records. This has been attributed to slight inescapable changes in the position of the precordial electrode. We therefore investigated the records of 92 patients with a small initial positive deflection on whom repeated electrocardiograms were obtained at varying intervals. In 71 of these this deflection remained 2 mm. or less in all records, although minor variations in size did occur. In the other 21 cases it varied back and forth from small to normal in serial records. In these 21 cases there was no correlation between changes in the size of the initial positive deflection and the amplitude of the succeeding negative deflection. It is possible that in many of these patients the variations were associated with changes in the heart muscle, for the patients included cases with coronary thrombosis and progressive coronary artery disease. In some, however, a change in the position of the electrode was probably the cause.

In 42 of the cases with a small initial positive deflection which had repeated electrocardiograms there were noted also variations in the amplitude of the intrinsic negative deflection. Yet in none of these did the former become greater than 2 mm. even when the latter doubled in size. We may conclude therefore that abnormal initial positive deflections may remain small, independent of change in the amplitude of the intrinsic deflection.

#### THE INITIAL POSITIVE DEFLECTION IN CORONARY THROMBOSIS; CLINICAL CORRELATION

Since absence of the initial positive deflection (absent  $Q_4$  of previous authors) has been emphasized as a diagnostic electrocardiographic sign of myocardial infarction, we have made a particular



study of this deflection in a large series of coronary thrombosis. In Table III we have arranged 261 consecutive cases of recent and old coronary thrombosis and have correlated the site of infarction with the presence or absence of this deflection. In 128 patients with infarction of the anterior surface of the heart, diagnosed by a typical electrocardiographic pattern ( $Q_1$   $T_1$  type), the initial positive deflection in the precordial lead was absent in slightly more than half the cases, small in one-sixth and normal in about one-third. In 78 patients with infarction of the posterior wall ( $Q_3$   $T_3$  type), it was normal in all but 11 cases; in 9 of these it was small and in only two was it absent. In 30 patients with signs of infarction of both anterior and posterior surfaces no clear cut division was found; the initial positive deflection was normal, small or absent, depending apparently upon which lesion exerted the predominant effect on the form of the electrocardiogram. It is noteworthy, however, that the frequency of absence of the initial positive deflection when the anterior and pos-

TABLE III

THE INITIAL POSITIVE DEFLECTION IN CORONARY THROMBOSIS (261 CASES)

| LOCATION OF INFARCTION | NO. OF CASES | INITIAL POSITIVE DEFLECTION |            |             |
|------------------------|--------------|-----------------------------|------------|-------------|
|                        |              | ABSENT                      | SMALL      | NORMAL      |
| Anterior wall          | 128          | 71 (55.0%)                  | 19 (15.0%) | 38 (30.0%)  |
| Posterior wall         | 78           | 2 (2.5%)                    | 9 (11.5%)  | 67 (86.0%)  |
| Anterior and posterior | 30           | 9 (30.0%)                   | 13 (43.0%) | 8 (27.0%)   |
| Undetermined location  | 25           | 0                           | 10 (40.0%) | 15 (60.0%)  |
| Total                  | 261          | 82 (31.0%)                  | 51 (19.5%) | 128 (49.0%) |

terior surfaces of the heart were involved was much smaller than when the infarction was limited to the anterior wall. An absent initial positive deflection in coronary thrombosis with but two exceptions (Fig. 15) occurred only when the anterior surface of the heart was damaged, whether this was the sole injury or whether the posterior wall also was involved. A small deflection, however, occurred almost as frequently in posterior as in anterior wall infarction (Fig. 4).

#### INITIAL POSITIVE DEFLECTION IN CORONARY THROMBOSIS; POST-MORTEM CORRELATION

The above conclusions were corroborated by the observations in 50 patients with coronary thrombosis in whom post-mortem examination was made (Table IV). There were 15 patients with anterior wall infarction; the initial positive deflection was absent in eleven, small in two and normal in the remaining two. In 13 patients with posterior wall infarction it was small four times and absent only once. However in the latter case the absent deflection may have resulted from an old partial occlusion of the left anterior descending coronary artery which was also present. When infarction of both anterior and

posterior walls was found (19 cases) the initial positive deflection was absent only four times and small in one-half of the cases. Again we note the smaller incidence of absence of the initial positive deflection when anterior wall infarction is accompanied by posterior wall infarction. Perhaps the latter sets up an electrical effect which balances that of the former, so that the QRS complex remains normal. In two cases of infarction of the lateral wall of the left ventricle and in one case of septal infarction without involvement of the anterior surface, the standard lead electrocardiogram showed a typical  $T_1$   $T_2$  pattern but a normal QRS was present in the precordial lead. It is thus evident that in coronary thrombosis absence of the initial positive deflection almost invariably denotes infarction of the anterior wall. However a normal initial positive deflection not infrequently occurs in the presence of infarction in this site, particularly when the posterior surface of the heart is involved simultaneously.

TABLE IV

THE INITIAL POSITIVE DEFLECTION IN ACUTE CORONARY THROMBOSIS  
(50 POST-MORTEM CASES)

| LOCATION OF INFARCTION        | NO. OF CASES | INITIAL POSITIVE DEFLECTION |            |            |
|-------------------------------|--------------|-----------------------------|------------|------------|
|                               |              | ABSENT                      | SMALL      | NORMAL     |
| Anterior wall                 | 15           | 11 (73.3%)                  | 2 (13.3%)  | 2 (13.3%)  |
| Posterior wall                | 13           | 1 (8.0%)*                   | 4 (31.0%)  | 8 (61.0%)  |
| Anterior and posterior wall   | 19           | 4 (21.0%)                   | 9 (47.5%)  | 6 (31.5%)  |
| Lateral wall (left ventricle) | 2            | 0                           | 0          | 2          |
| Anterior septum               | 1            | 0                           | 0          | 1          |
| Total                         | 50           | 16 (32.0%)                  | 15 (30.0%) | 19 (38.0%) |

\*Plus old partial thrombosis of left anterior descending without anterior wall infarction.

#### SMALL INITIAL POSITIVE DEFLECTION; POST-MORTEM OBSERVATIONS

It has already been shown that when the initial positive deflection is small, clinical or electrocardiographic evidence of myocardial damage is usually present. In our opinion, a small initial positive deflection is almost as significant as an absent one, and the post-mortem observations in 26 patients with this finding (Table II) support this view. Fifteen of these showed evidence of myocardial infarction, recent or old. However, in contrast to an absent initial positive deflection, a small one did not tend to localize the infarction to the anterior surface. In only two of these fifteen patients was the infarction limited to the anterior wall; in five it was solely posterior; and in eight, both anterior and posterior. Of the eleven patients without infarction ten showed definite myocardial involvement due to coronary sclerosis or to valvular disease. In only one was the heart muscle normal. Levine and Levine<sup>22</sup> similarly found myocardial infarction in one-half of a group of fifteen patients with a small initial deflec-

tion examined post mortem. The post-mortem observations of these authors and our own lead to the conclusion expressed previously that a small initial positive deflection nearly always indicates myocardial involvement and usually is associated with recent or old coronary thrombosis, whatever the site of infarction.

#### SIMPLE CHEST ELECTRODE VERSUS "ZERO POTENTIAL" LEAD

Recently Wilson and his associates<sup>19</sup> and Kossman and Johnston<sup>12</sup> have employed the so-called "zero potential" lead to exclude any possible effects of the indifferent electrode. They pair the precordial electrode with a central terminus which is connected through three large and equal resistances to both arms and left leg. They regard the potential of this terminus as practically zero throughout the cardiac cycle and the curve obtained to represent the potential variations of only the precordial electrode. These investigators point out that the potential of the left leg which is the site of the indifferent electrode may be great enough to alter the appearance of the precordial lead. Thus it is claimed that if the initial positive deflection is small when the precordial lead is obtained by the ordinary method, it may at times be absent if the "zero potential" method is used. This may be theoretically correct but actually we found little difference when the precordial lead was recorded with both methods in the same patient.

In 28 cases with a normal QRS group in the precordial lead, the latter was taken in the five positions over the chest wall as previously described, with both the "zero potential" and the ordinary simple electrode. Although slight differences in voltage were observed, in no instance did a normal initial positive deflection become small or disappear when the lead was recorded by the Wilson technique. Similarly, no change occurred in 9 patients with myocardial damage in whom this deflection was small. A few variations, however, were found in a group of 27 patients with an absent initial positive deflection. In five instances the "zero potential" lead presented a small instead of absent deflection in all or some of the chest positions. The diagnoses in these 5 patients were respectively recent coronary thrombosis, old coronary thrombosis, rheumatic aortic insufficiency, spontaneous pneumothorax, and acute myocarditis of uncertain etiology.

It appears to us from these observations that the "zero potential" possesses no diagnostic advantage over the routine method, so far as the initial positive deflection is concerned. The greatest change, from an absent to a very small deflection, was not common. Furthermore, the significance of a very small deflection is almost as great as that of an absent one.

## CAUSE OF ABSENT INITIAL POSITIVE DEFLECTION

Wilson and his associates<sup>16-21</sup> believe that absence of the initial positive deflection is due to the presence of an area of dead or inactive tissue on the anterior surface or apical region of the heart. They, as well as Bellet and Johnston,<sup>4</sup> have demonstrated that absence of the initial positive deflection was a constant late finding in direct and indirect leads from a dog's heart after ligation of the left anterior descending coronary artery. They attributed this to the fact that since the infarcted area no longer responded to the stimulus there was no difference in potential between the endocardial and epicardial surfaces. The electrocardiogram therefore resembled one obtained by leading off directly from the ventricular cavity in which the QRS group consists only of a large negative deflection. Levine and Levine<sup>22</sup> agreed that absence of the initial positive deflection was nearly always due to myocardial infarction but did not explain its absence in their cases of bundle-branch block and pericarditis. On the other hand, Frucht<sup>25</sup> believed that enlargement of the left ventricle, by causing rotation of the heart, could produce absence of this deflection. However, because of his lack of post-mortem evidence and since the initial deflection frequently remains normal in spite of considerable cardiac enlargement, this view has not been accepted. Our results tend to show that both these factors, anterior wall infarction and cardiac rotation or enlargement, may be significant. Obviously in the cases of pneumothorax there was no myocardial involvement, but the hearts were definitely rotated and displaced. When the cardiac axis returned to normal, the QRS group in the precordial lead also became normal. Furthermore, the cases of rheumatic valvular disease in young individuals with a large heart and absent or small initial deflection cannot be explained on the basis of myocardial infarction. Similarly in acute nephritis we have shown<sup>26, 27</sup> that there are no gross anatomical changes in the myocardium and the absence of the initial positive deflection must be explained on the basis of capillary damage. Nevertheless, we agree with Wilson that in the great majority of instances the cause for disappearance of this deflection is myocardial infarction.

What has been said of an absent initial positive deflection applies also to a small one. The conditions associated with absence of this wave may cause instead a marked diminution in its size. Indeed, a small deflection may at times disappear and reappear in the same record. Therefore a small initial deflection probably has a significance similar to that of an absent one.

## SUMMARY

1. The initial positive deflection in the precordial lead (Q-wave of old, R-wave of new technique) was absent in 2.7 per cent of 4,500 consecutive hospital patients and was small (2 mm. or less) in 3.9 per cent.

2. In two-thirds of the patients, absence of this deflection was associated with recent or old coronary thrombosis and anterior wall infarction, and in one-fifth, with coronary artery disease alone, with or without hypertension.

3. The initial positive deflection was also absent in 14 cases diagnosed as acute and chronic glomerulonephritis, rheumatic and syphilitic valvular disease, pneumothorax, Graves' disease, and acute myocarditis. There was no evidence of myocardial infarction in these cases.

4. In patients with an M or W-shaped QRS complex preordial leads obtained from other positions on the chest wall usually demonstrated absence of the initial positive deflection. This holds frequently when a large initial negative deflection precedes a large positive deflection.

5. Absence of this deflection was permanent in the majority of cases even when an abnormal  $T_4$  and abnormal standard leads returned to normal.

6. Absence of the initial positive deflection was accompanied by an abnormal  $T_4$  in 54 per cent of cases.

7. Of the patients with a small initial positive deflection 7.5 per cent had no clinical evidence of cardiovascular disease. The remainder suffered from coronary thrombosis (29 per cent), coronary artery disease with or without hypertension (37 per cent), rheumatic valvular disease (17 per cent), miscellaneous heart involvement (12 per cent). These included cases of intraventricular or bundle-branch block.

8. In only one-fifth of these patients was there an associated abnormal T-wave in the precordial lead. A small initial positive deflection was significant when followed by an intrinsic deflection of at least 10 mm.

9. In a large group of cases with anterior wall infarction, diagnosed electrocardiographically or at autopsy, the initial positive deflection was absent in more than one-half, small in one-sixth, and normal in one-third. In posterior wall infarction this deflection was rarely absent but was frequently small.

10. In 26 patients with a small initial positive deflection, myocardial infarction was found 15 times. Only one case showed normal heart muscle.

11. Comparison of the ordinary method of recording the preordial lead with the "zero potential" method of Wilson revealed no practical advantage of the latter as far as diagnosis was concerned.

#### CONCLUSION

The precordial lead has become increasingly important in electrocardiographic diagnosis, not only in coronary thrombosis but also in involvement of the heart in other conditions. It is not infrequently abnormal when the standard leads appear normal. The most significant

change in the precordial lead is absence of the initial positive deflection which may occur even when the T-wave remains normal. An absent initial positive deflection is the most reliable sign of myocardial infarction and, with rare exceptions, localizes the infarct in the anterior wall of the heart. Although it reappears in a small number of cases, it usually remains absent permanently and may be the only electrocardiographic sign of previous infarction. A small initial positive deflection may have the same significance as an absent one; however, it is less specific than the latter and does not indicate the site of infarction. It is nearly always an abnormal finding.

Hitherto the relation of the absence of the initial positive deflection to coronary thrombosis alone has been considered important. However, this study emphasizes the significance of an absent or small deflection in various other diseases which lead to damage of the myocardium or to enlargement or change in position of the heart. Therefore, while an abnormal initial positive deflection is, in most cases, indicative of myocardial infarction, it should no longer be regarded as pathognomonic of this condition.

#### REFERENCES

1. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, *Am. J. M. Sc.* 183: 30, 1932.
2. Wolferth, C. C., and Wood, F. C.: Further Observations on the Use of Chest Leads in Electrocardiographic Study of Coronary Occlusion, *M. Clin. North America* 16: 161, 1932.
3. Wood, F. C., Bellet, S., McMillan, T. M., and Wolferth, C. C.: Electrocardiographic Study of Coronary Occlusion. Further Observations on the Use of Chest Leads, *Arch. Int. Med.* 52: 752, 1933.
4. Bellet, S., and Johnston, C. G.: The Effect of Coronary Occlusion Upon the Initial Phase of the Ventricular Complex in Precordial Leads, *J. Clin. Investigation* 13: 725, 1934.
5. Wood, F. C., and Wolferth, C. C.: Huge T-waves in Precordial Leads in Cardiac Infarction, *AM. HEART J.* 9: 707, 1934.
6. Katz, L. N., and Kissen, M.: A Study of Lead IV. Its Appearance Normally, in Myocardial Disease, and in Recent Coronary Occlusion, *AM. HEART J.* 8: 595, 1933.
7. Liberson, A., and Liberson, F.: The Value of Posterior-Anterior Chest Leads in Cardiac Diagnosis, *Ann. Int. Med.* 6: 1315, 1933.
8. Hoffman, A. M., and DeLong, E.: Standardization of Chest Leads, *Arch. Int. Med.* 51: 947, 1933.
9. Master, A. M.: The Precordial Lead in 104 Normal Adults, *AM. HEART J.* 9: 511, 1934.
10. Goldbloom, A. A.: Clinical Evaluation of Lead IV (Chest Lead). A Survey of Lead IV in Ambulatory Cases of Coronary Artery Disease and Acute Coronary Occlusion, *Am. J. M. Sc.* 187: 489, 1934.
11. Bohning, A., and Katz, L. N.: The Four-Lead Electrocardiogram in Coronary Sclerosis, *Am. J. M. Sc.* 189: 833, 1935.
12. Roth, I. R.: On the Use of Chest Leads in Clinical Electrocardiography, *AM. HEART J.* 10: 798, 1935.
13. Kossman, C. E., and Johnston, F. D.: The Precordial Electrocardiogram. 1. The Potential Variations of the Precordium and of the Extremities in Normal Subjects, *AM. HEART J.* 10: 925, 1935.
14. Shipley, R. A., and Hallaran, W. R.: The Four-Lead Electrocardiogram in Two Hundred Normal Men and Women, *AM. HEART J.* 11: 325, 1936.
15. Master, A. M., Dack, S., and Jaffe, H. L.: Chest Leads in Normal Children, *Proc. Soc. Exper. Biol. & Med.* 32: 1529, 1935.

16. Wilson, F. N., Barker, P. S., Macleod, A. G., and Klostermeyer, L. L.: The Electrocardiogram in Coronary Thrombosis, *Proc. Soc. Exper. Biol. & Med.* 29: 1006, 1932.
17. Wilson, F. N., Macleod, A. G., Barker, P. S., and Klostermeyer, L. L.: The Electrocardiogram in Myocardial Infarction With Particular Reference to the Initial Deflections of the Ventricular Complex, *Heart* 16: 155, 1933.
18. Wilson, F. N., Johnston, F. D., Hill, I. G. W., and Grout, G. C.: The Electrocardiogram in the Later Stages of Experimental Myocardial Infarction, *Tr. A. Am. Physicians* 48: 154, 1933.
19. Wilson, F. N., Johnston, F. D., Macleod, A. G., and Barker, P. S.: Electrocardiograms That Represent the Potential Variations of a Single Electrode, *AM. HEART J.* 9: 447, 1934.
20. Wilson, F. N., Hill, I. G. W., and Johnston, F. D.: The Form of the Electrocardiogram in Experimental Myocardial Infarction. III. The Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, *AM. HEART J.* 10: 903, 1935.
21. Wilson, F. N.: The Electrocardiogram in Diseases of the Coronary Arteries. In Levy, R. L.: *Diseases of the Coronary Arteries and Cardiac Pain*, New York, 1936, The Macmillan Company.
22. Levine, H. D., and Levine, S. A.: An Electrocardiographic Study of Lead IV With Special Reference to the Findings in Angina Pectoris, *Am. J. M. Sc.* 191: 98, 1936.
23. Levine, H. D.: Effect of Various Altered Cardiac Mechanisms on Lead IV. *M. Papers Christian Birthday Vol.* p. 87, 1936.
24. Groedel, F. M.: Das über dem rechten und linken Ventrikel abgeleitete Elektrokardiogramm, *Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch.* 6: 127, 1933.
25. Frucht, S.: Lead IV of the Electrocardiogram, *Med. Times and L. I. Med. J.* 61: 232, 1933.
26. Master, A. M., Jaffe, H. L., and Dack, S.: The Electrocardiogram in Acute Nephritis, *AM. HEART J.* 12: 244, 1936.
27. Master, A. M., Jaffe, H. L., and Dack, S.: The Heart in Acute Glomerulonephritis, *In Press*.
28. Master, A. M.: The Electrocardiographic Changes in Pneumothorax in Which the Heart Has Been Rotated. The Similarity of Some of These Changes to Those Indicating Myocardial Involvement, *AM. HEART J.* 3: 1, 1928.
29. Jervell, A.: Elektrokardiographische Befunde bei Herzinfarkt, *Acta Med. Scandinav. Supplement* 68, 1935.

## SOME EFFECTS OF ALTERATION OF POSTURE ON ARTERIAL BLOOD PRESSURE\*

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THAT gravity has an influence on the distribution of blood in the body has long been recognized and most of the fundamental points are brought out in the papers of Hill,<sup>1</sup> and Hill and Barnard.<sup>2</sup> References to the earlier literature (Priory, 1826, Hall, 1832, and others) are found in these papers of Hill. These earlier observers found, for example, that if a dog or man were bled in the vertical position until syncope occurred, then recovery followed on placing the subject in a horizontal position. Hill, however, carried out a very comprehensive set of experiments on rabbits, cats, dogs, and monkeys which showed, among other things, that the force of gravity must be regarded as a cardinal factor in dealing with the distribution of the blood; that the important duty of compensating for the simple hydrostatic effects of gravity in changes of position must be ascribed to the splanchnic vasomotor mechanisms; that the amount of compensation depends largely upon individual differences; that the compensation is far more complete in upright animals, such as the monkey, than in rabbits, cats, or dogs, and therefore is probably far more complete in man; that in some normal monkeys overcompensation for the hydrostatic effect occurs; that in the normal monkeys and man, gravity exerts but little disturbing influence, owing to the perfection of the compensatory mechanism; that when the power of compensation is damaged by paralysis of the splanchnic vasoconstrictors, induced by severe operative procedures or by injuries to the spinal cord, by asphyxia, or by some poison such as chloroform or curare, then the influence of gravity becomes of vital importance; that the feet-down position is of far greater moment than the feet-up position, because when the power of compensation is destroyed, the blood drains into the abdominal veins, the heart empties, and the cerebral circulation ceases; that firmly bandaging the abdomen prevents the drop of pressure when the animal is turned feet down; that if the heart is affected, as by chloroform or curare poisoning, the restoration of pressure is incomplete; that vagus inhibition and the cardiac acceleration are subsidiary compensatory mechanisms in the feet-up and the feet-down positions respectively; that chloroform rapidly paralyzes the compensatory vasomotor mechanism and damages the heart; that ether, on the other hand, only paralyzes the compensatory vasomotor mechanism very slowly and when pushed in enormous amounts; that chloroform can, by destroying the compensation for gravity, kill the animal if

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it be placed with abdomen at a lower level than the heart but that elevation or compression of the abdomen immediately compensates for the vasomotor paralysis produced by chloroform.

Since the taking of blood pressure on man became a common procedure a number of studies on the effects of changing posture in man have been made which will be referred to later. In such experiments the blood pressure was taken in one position and then again after the change. There was usually about a minute or more between the readings. Now Hill's tracings show the adjustments are very rapid and that much can occur in a minute. It seemed desirable, therefore, to obtain information about changes occurring in man in short intervals of time. In the arrangements we have used we can get three or four readings of blood pressure in a minute and are therefore better able to follow the adjustments.

#### THE MEASUREMENT OF BLOOD PRESSURE

There are various factors to be considered in the measurement of blood pressure; such as the experimental error of the observer, and the instrumental error of the sphygmomanometer. In all of the work done here the Tyco's self-recording sphygmomanometer was used. The bag was attached to the upper arm and the arm not moved in its relation to the thorax during the course of the experiment. This machine was thoroughly tested and the results obtained indicated that the blood pressures measured upon it are entirely comparable, within the range of normal, to those taken by the more common auscultatory methods. The advantages of this instrument are: some elimination of the personal error in the measurement of blood pressure since the recordings are mechanical, and the possibility of making rapidly repeated measurements of blood pressure—as many as three or four per minute—merely by moving the writing stylus on the same chart. The instrumental error in this type of machine is relatively small, averaging about 2 to 4 mm. Hg. The conditions of the experiment were kept as nearly the same for different subjects as possible.

One point which is generally not considered in the taking of blood pressure is the effect of the painful stimulus resulting from congestion in the arm. In order to reduce this to a minimum, the cuff should be inflated as rapidly as possible to a point 20 to 30 mm. Hg above the expected systolic blood pressure, and the deflation started immediately upon the completion of inflation. This was accomplished by means of a simple apparatus as follows: Compressed air is led into a large (8 liter) bottle provided with two outlets. One outlet is attached to an adjustable mercury valve so that the pressure may be kept at any desired level in the bottle. A tube provided with a stopcock connects the other outlet of the bottle to the arm cuff. The cuff is inflated practically instantaneously by turning the stopcock. By this quick inflation there is virtually

no venous congestion and thus less pain and unpleasantness. As soon as the cuff is inflated the stopcock to the pressure bottle is closed and the deflation of the cuff started immediately.

In our experience at least three trials were found to be necessary before a subject became sufficiently accustomed to the experimental procedure to show cardiovascular measurements at a basic level. There was always a certain amount of excitement present in the first trials which showed chiefly in the high pulse rate.

Our own work on the change in posture may be divided into three parts. (1) The immediate effect, i.e., during the first minute; (2) the prolonged effect after the first minute; (3) experiments on animals trying to determine the mechanisms of adjustments.

### *1. Immediate Effects*

*When the Subject Stood Up.*—These changes were studied by allowing the subject first to rest in the reclining position until the blood pressure became stable. This usually did not take longer than five minutes. The subject was then told to stand up with as little effort as possible, and a series of blood pressure records was taken rapidly. The accuracy of the recording sphygmomanometer depends on adjusting the apparatus to the heart rate. The heart rate always increases on standing. In the first trials the recumbent and standing rates were determined and the machine set at the expected standing rate. The first systolic record was obtained about ten seconds after the change in position had taken place, the second systolic record at about twenty to thirty seconds after the change, and the third systolic record forty-five to sixty seconds after the change. The diastolic records appeared some five to ten seconds after the corresponding systolic records. This procedure was carried out on a good number of normal individuals, chiefly medical students, nurses, and instructors.

The results obtained on persons with normal pressures may be seen graphically in Figs. 1 and 2. Fig. 1 shows the resulting reaction on systolic pressure of 14 individuals. In this chart the vertical lines indicate thirty-second intervals while the horizontal lines represent 10 mm. of mercury pressure. The values for the three readings after the changes are indicated and the points joined. We have no proof that the blood pressure exactly followed these lines.

With one exception the first systolic record after the change was lower than the reclining systolic pressure, the amount of the drop varying in different individuals from 5 to 40 mm. Hg. After the initial drop the curves are different as may be seen from the charts. Within thirty seconds the majority of the subjects had a systolic pressure higher than the reclining. At sixty seconds this majority was somewhat lessened. The lowest point in the blood pressure occurs about ten seconds after the change. If in the same individual pressures are obtained at seven

or eight seconds or about twelve seconds after the change, the drop is usually not as great as that obtaining at ten seconds. The diastolic pressure at the first reading showed a rise, as compared to the reclining diastolic pressure, in about 76 per cent of the individuals tested. The pressure fell in approximately 18 per cent and in 6 per cent it remained unchanged. These percentages did not change significantly after the first reading. In four individuals this procedure was repeated several times, in an effort to time the readings so as to have more points on the curve. When the curve is filled in (Fig. 2, light lines) it does not differ significantly from that obtained by joining the three points. In this chart the diastolic pressures are also shown.

Among those tested was one of the "ends" of the football team. These tests were run in the midst of the football season and might therefore be said to be on an individual in the best condition obtainable by training. His results showed the same reactions as those of an untrained individual.

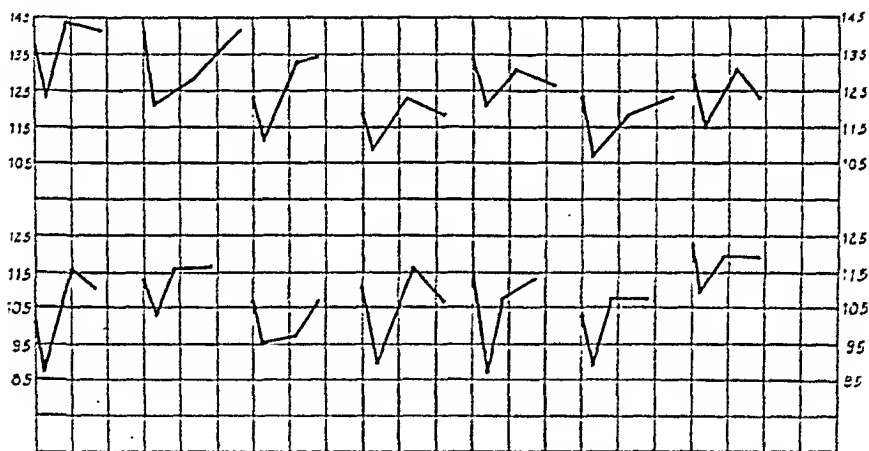


Fig. 1.—Systolic pressures on changing from recumbent to standing position. Fourteen adult males. Vertical lines represent thirty-second intervals; transverse lines, 10 mm. Hg pressure.

Among the students tried was one with a high reclining pressure (158 systolic). Although we tried three times we could never get a lower systolic pressure when he stood than the reclining value. We do not know if it is characteristic of people with high blood pressures to react in this manner. Hill mentions a monkey in which the same phenomenon occurred. We are also not sure about the accuracy of the sphygmomanometer at this level.

Thus we see that with a change in position from reclining to standing there is a sharp drop in systolic pressure along with a slight rise in diastolic pressure. Very quickly in most cases the systolic pressure recovers a large percentage of this drop, and in many instances exceeds the original reclining systolic value. For the majority of individuals this is complete within thirty seconds. At sixty seconds the height of systolic

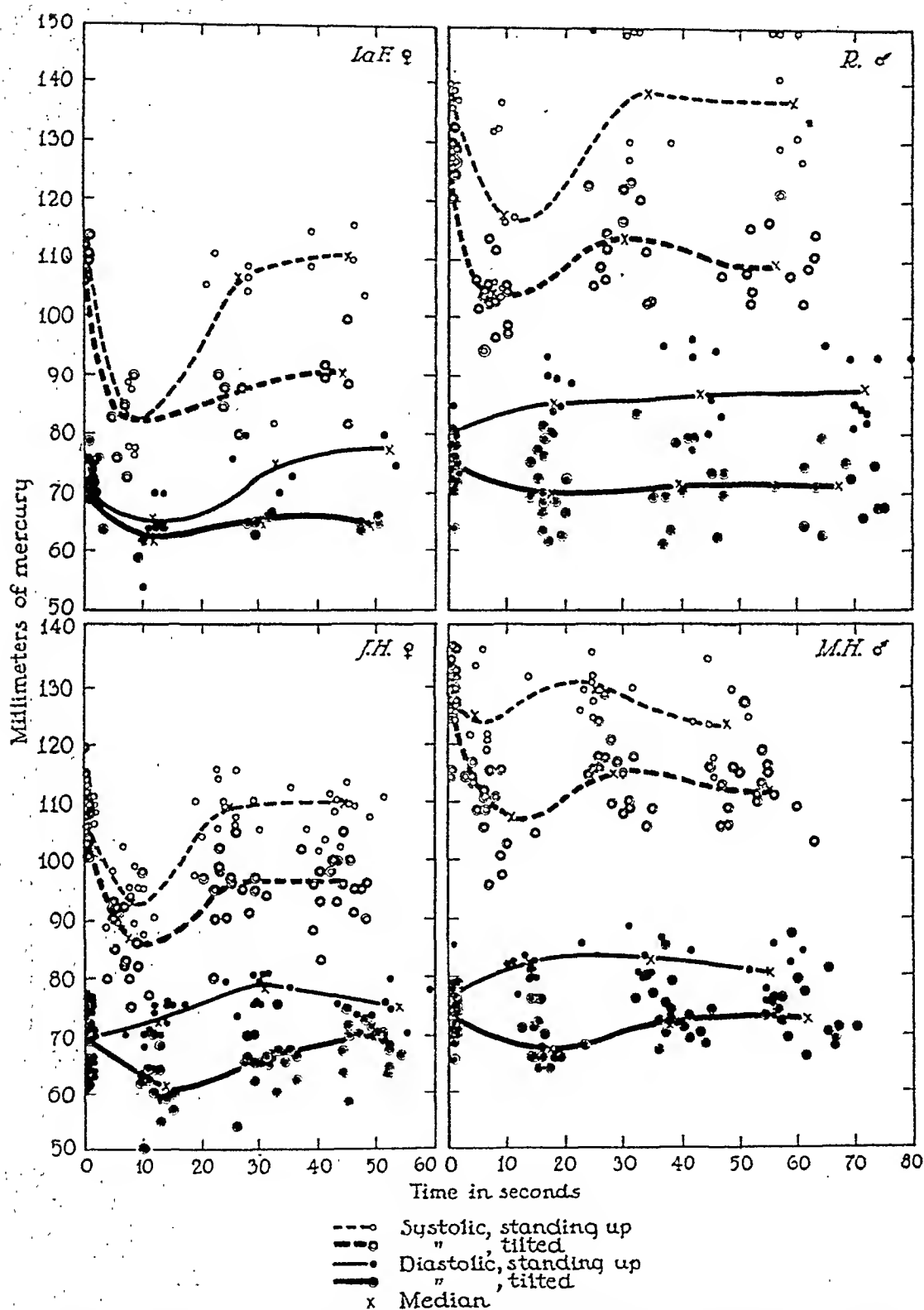


Fig. 2.—Systolic and diastolic pressures on changing from recumbent to standing (light lines) and tilting positions (heavy lines) repeated on 2 males and 2 females.

pressure is somewhat lessened. The sequence of events seems to be as follows: the change in position by a simple physical process due to the shifting of the blood into the abdominal cavity causes a sharp drop in systolic pressure. Very soon after this has happened the process of com-

pensation begins; reflexly, as will be shown later. This compensation, on the average, reaches its maximum effect within thirty seconds after the change in position, and at this point the indications are that a slight overcompensation exists, and that the normal level for standing is reached approximately after one minute.

*When the Subjects Were Tilted.*—Measurements were made in the same way upon the same group of subjects when they were tilted from



Fig. 3.—Systolic and diastolic pressure changes on tilting from recumbent to vertical position. Upper figures represent 8 different females and 8 different males. Lower figures represent repeated tilts on same subjects. Vertical lines represent fifteen-second intervals.

the horizontal to the vertical instead of standing. The subjects were so adjusted on the tilting board that the arm bag remained at the level of the heart. The results may be seen in Fig. 2 (heavy lines) and in Fig. 3. Fig. 2 represents the results of standing and tilting repeated on the same individuals a number of times, while Fig. 3 shows the result of tilting on 8 men and 8 women, and the results of tilting two individuals (a male and female) a number of times. In both charts systolic and diastolic pressures are shown. It will be noted that the systolic drop of

pressure is greater on tilting than on standing and that the amount of compensation which followed the initial drop is less. In no case was the systolic pressure at the end of thirty seconds higher than the reclining pressure, as was the case in standing. At the end of sixty seconds the systolic pressure was much less than the reclining level and the diastolic pressure was in most cases less than the reclining, while it was higher when the person stood up. The only explanation for the differences in the reaction to the change of position is that the differences were due to the muscular effort involved in standing up. When a person stands from the reclining position there occur strong contractions of abdominal muscles. This would increase intra-abdominal pressure, improve the venous return to the heart, and aid in the compensatory return of the blood pressure level. This factor is not present in tilting and probably accounts for the greater part of the difference in the response of these two methods of changing the position of the body from the horizontal to vertical.

*The Effect of the Change in Position From Vertical to Horizontal by Tilting.*—In order to determine the effect of a change in position from vertical to horizontal the subject was started in the horizontal position as in the previous experiments. He was then tilted into the vertical position and allowed to remain there until the blood pressure was stable over a three-minute period (no changes greater than three mm. Hg from minute to minute). After this point had been reached the subject was tilted back into the horizontal position and a series of blood pressure measurements were taken, three within the first sixty seconds, more or less, then one every minute until five minutes had elapsed. Usually by this time the values rather closely approximated the previous reclining record. This procedure was carried out on two subjects, seven times on one and four times on the other. The reaction of the two subjects, as may be seen from Fig. 4, differed somewhat. In one subject there was a very sharp rise of systolic pressure with the reverse tilt, to a level considerably higher than the original reclining level. The systolic pressure then gradually fell until finally after a few minutes it was approximately equal to the former reclining level. In this subject the diastolic pressure rose slightly and then fell to the former reclining level. As a result there was a rapid rise in pulse pressure to a level higher than the former reclining one, with a gradual decrease after this until the former reclining level was reached. On the other hand, the second subject, when tilted from the vertical to the horizontal position, showed a very sluggish rise in systolic pressure, and the reclining level was reached only after a minute had passed. At no time did the systolic pressure greatly exceed the former reclining level. However, with the shift in position there occurred a considerable drop in diastolic pressure, which after a period of time showed a tendency to recover toward the

former reclining level. This return was not completed within five minutes. However, the pulse pressure curve in this case was somewhat similar to that in the first case. Therefore, one might say that although the mechanism in these cases differed, the results upon the circulation,

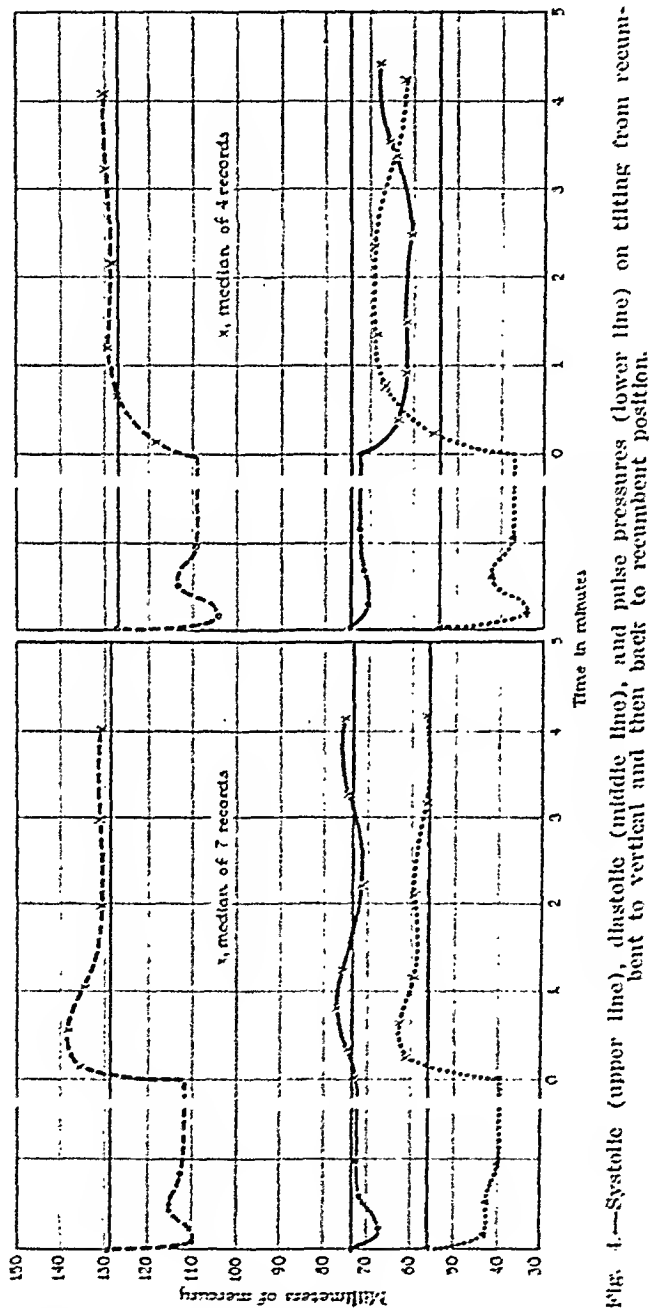


FIG. 4.—Systolic (upper line), diastolic (middle line), and pulse pressures (lower line) on tilting from recumbent to vertical and then back to recumbent position.

in terms of pulse pressure, were about the same. The curves bring out the point noted before, namely, that no two subjects react exactly alike.

## 2. The Course of the Blood Pressure

*After the First Minute in Subjects Who Stood Up.*—In a study of the effect of controlled exercise upon physical efficiency over 300 male, fresh-

man, students were given a modification of the Turner test.<sup>3</sup> The Turner test, which is a cardiovascular test of physical efficiency, is based upon the reactions of the blood pressure and pulse rate to the change in position from reclining to standing, and the effect of prolonged quiet standing upon blood pressure and pulse rate. In the modification of the test used here the blood pressure was measured first in the reclining position after the subject had been reclining for at least five minutes. Then the subject arose with as little effort as possible and a series of blood pressure records were made, one each minute for the first three minutes, then one every other minute until fifteen minutes had elapsed. Many of the subjects exhibited signs of excitement during the first trial. This shows up most in the heart rate. Although the blood pressure had ceased to fall after five minutes of reclining, the pulse rate on the first trial averaged 75 for all the subjects, 69 on the second trial, and 63 on the third trial. On trying a number of students a fourth and fifth time there was practically no change from the third trial. After one minute of standing the rates were 91, 88, and 84 for the three trials. The data presented on the pressure changes are from the third trial. One minute after the change in posture 31.6 per cent of this group of over 300 who took the test had a systolic blood pressure higher than the reclining level, 58.7 per cent had a systolic pressure lower than the reclining, and 9.7 per cent remained the same. In the case of the diastolic pressure 82.7 per cent were higher than the reclining level, 9.7 per cent were lower, and 7.6 per cent remained unchanged. In both systolic and diastolic pressures these percentages did not change significantly within the first three minutes, and the average level of blood pressure also did not change significantly within the first three minutes. Furthermore, the average blood pressure remained practically constant for the remainder of the fifteen-minute period. The greatest variation from average to average was less than  $\frac{1}{2}$  mm. Hg. These records indicate further that the compensatory changes of blood pressure to the change in posture from reclining to standing are completed within the first minute. Of course, in some individuals this may not be the case, but it certainly is for any large normal group as well as most normal individuals. The percentage of individuals having a higher systolic pressure on standing (31.6 per cent) is less than that found by most others. Schneider and Truesdell,<sup>4</sup> on 2,000 cases of students, found 55.5 per cent had a higher standing systolic pressure than recumbent and only 26.5 per cent a lower. We believe this is because there was probably less excitement connected with our tests and we may have had a better selected group. The figure given by Schneider and Truesdell (55.5 per cent higher systolic pressure) corresponds more to our unselected group described in the first part of this paper.

Prolonged quiet standing may be a severe strain on the circulatory system of many normal individuals since it is not extremely rare to find



seemingly normal individuals faint before fifteen minutes is over. Turner also observed this with some of her subjects. In the course of this experiment each subject was tested three times. Since there were approximately 300 subjects a total of 900 tests were made. During the course of these 900 tests, although we had a selected group, some 40 faintings were observed, about one in each 22 tests. However, 25 of these faintings occurred in the first trial, 10 in the second, and only 5 in the third. One subject fainted in all three trials, a few fainted in two trials but most fainted only once in the three trials. Fainting as a reaction to prolonged quiet standing in this test might be classified as a result of two primary causes. First, in the great majority of the subjects who faint in the first trial and then reacted normally in the

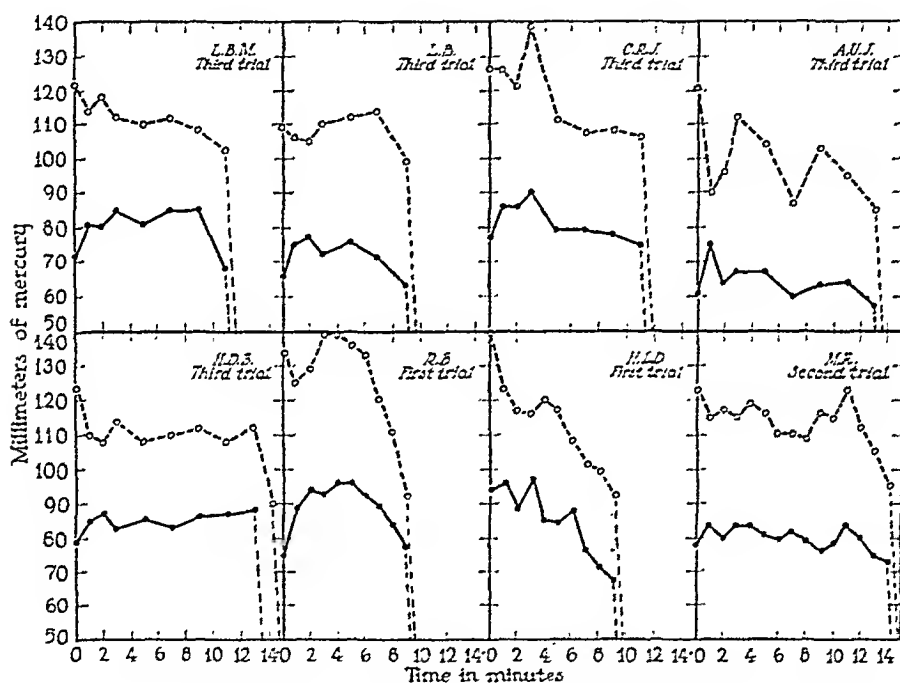


Fig. 5.—Systolic and diastolic pressure changes during quiet standing preceding fainting.

subsequent trials, the fainting undoubtedly had a psychogenic basis. In other words, the nervousness or apprehension of the subject who was unfamiliar with this type of examination affected directly or indirectly the cardiovascular reactions in such a manner as to produce a sudden drop in blood pressure. This resulted in fainting. When these subjects became familiar with the test, and the fear was lost, they reacted normally. The second primary cause of the fainting was an inadequate cardiovascular regulating mechanism. In these subjects the faints occurred more than once, or in the trials in which they did not faint they showed great instability in their reaction to change in posture and quiet standing. In these cases the fainting was undoubtedly due to the inability of the cardiovascular system to remain compensated during a

period of prolonged quiet standing. In most of the subjects who fainted the systolic pressure kept dropping for a number of minutes before the faint but in a few subjects the drop was very rapid as may be seen from the chart.

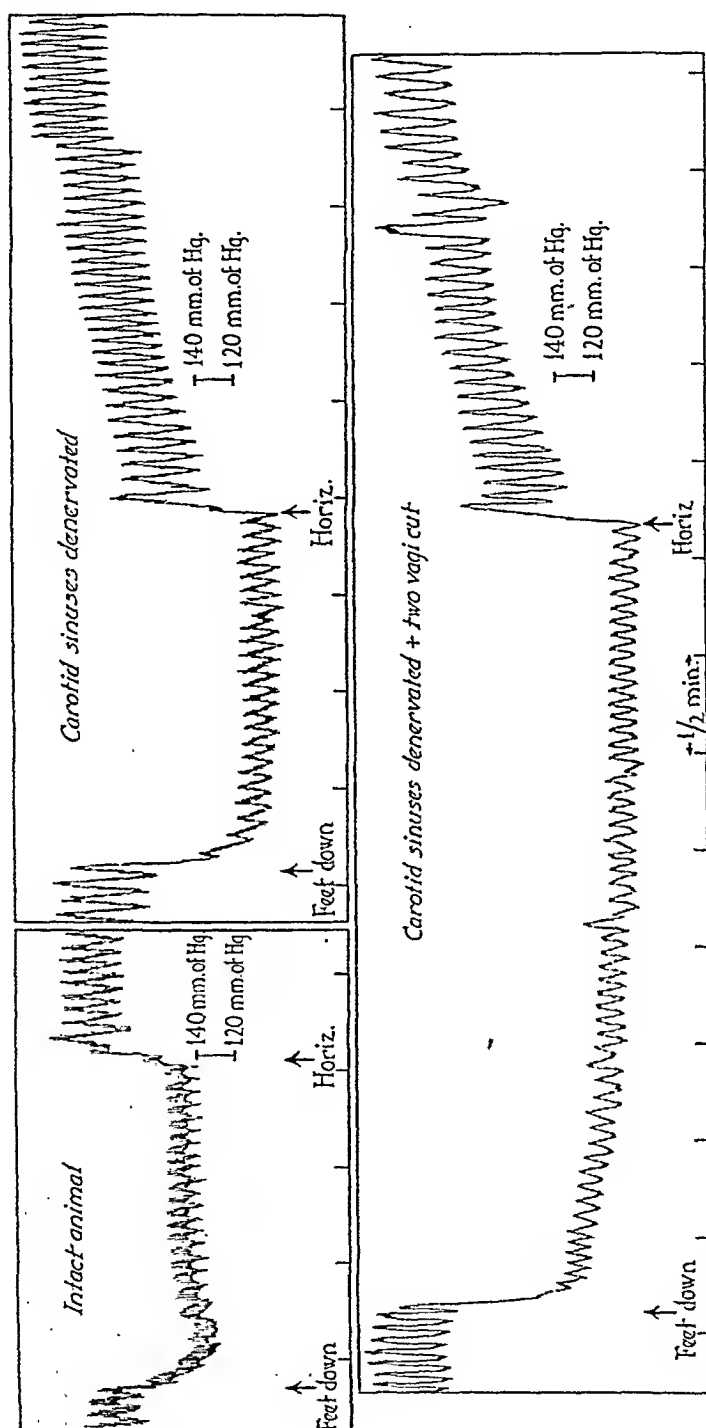


Fig. 6.—Blood pressure changes in dog (morphine-ether anesthesia) on turning from horizontal to feet-down position on (a) intact animal; (b) after denervation of carotid sinuses; (c) after denervation of carotid sinuses and section of both vagi.

### 3. Experiments on Animals

It seemed probable that reflexes are responsible for the readjustment in the pressure on standing and to test this matter experiments were made on dogs using Hill's technique.<sup>1</sup> Most dogs when they are tilted from the horizontal to feet-down position show the drop of pressure

with little or no tendency for the pressure to rise no matter how long the animal is kept in the vertical position, as can be seen in Fig. 6. Occasionally one finds a slight compensatory rise but we have never seen anything comparable to that found in man.

We tried animals under morphine-ether, sodium amytal, and after decerebration. However, that, even in the dog, reflexes are tending to keep up the pressure can be seen from the effects of denervating the carotid sinuses and section of the vagi. It will be noticed that the drops of pressure are greater and steeper than before and any slight tendency toward compensation is lost. Edholm and McDowall<sup>5</sup> state that denervation of the carotid sinuses makes no difference in the gravity effect. In our work on some 25 dogs the above mentioned differences have always been noted.

#### SUMMARY

On changing from the recumbent to standing position the systolic pressure is from 5 to 40 mm. Hg below the recumbent level about ten seconds after the change. There is a rapid recovery after this initial drop and after about thirty seconds many have regained or passed the recumbent level. In some few cases the recovery is slower. Diastolic pressure usually rises slightly on standing. The same type of reaction is seen when the subjects are tilted into the vertical posture but the drop is greater and the recovery less. Prolonged quiet standing is a severe strain on the circulation as shown by the frequency of fainting. Reflexes from the carotid sinuses and arch of aorta are responsible (in part at least) for the reactions leading to the recovery of the pressure.

#### REFERENCES

1. Hill, L.: *J. Physiol.* 18: 15, 1895.
2. Hill, L., and Barnard, H.: *J. Physiol.* 21: 1, 1896.
3. Turner, A. B.: *Am. J. Physiol.* 80: 601, 1927; 81: 197, 1927; 87: 667, 1928; 94: 507, 1930.
4. Schneider, E. C., and Truesdell, D.: *Am. J. Physiol.* 61: 429, 1922.
5. Edholm, O., and McDowall, R. J. S.: *J. Physiol.* 86: 8p, 1936.

# AN ANALYSIS OF THE DIAGNOSTIC CRITERIA OF ANGINA PECTORIS

## A CRITICAL STUDY OF 100 PROVED CASES\*

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**H**EBERDEN'S classic description of angina pectoris<sup>1</sup> portrays the clinical characteristics so vividly that typical instances can be recognized without difficulty. Experience discloses, however, many variations of the clinical picture; furthermore, symptoms closely simulating angina occur in patients without heart disease. As a result, it is frequently difficult or even impossible to be certain of the diagnosis.

It is generally agreed that observation of the patient during an attack is a valuable aid in diagnosis. The majority of descriptions, including that of Heberden, are based not on actual observation, but on information obtained from patients suffering from the condition. The purpose of the present communication is to compare the patients' descriptions with observations made during actual attacks of angina pectoris in order to establish the criteria for diagnosis and to determine the frequency of atypical forms of the syndrome.

### METHOD OF STUDY

During the past four years approximately two hundred patients suspected of having angina pectoris were referred for diagnosis and study from the out-patient department, the medical wards, and the private practice of local physicians. A detailed clinical history was obtained by at least two independent observers and a thorough physical examination with special reference to the heart was performed. A determination of the blood hemoglobin and blood Wassermann reaction was made in each instance, and further blood studies were performed when indicated. Electrocardiographic studies and measurements of the heart size from seven-foot roentgenograms were made in most instances. The basal metabolic rate<sup>2</sup> and the serum cholesterol<sup>3</sup> were measured in many of the patients.

The reaction of the patient to exercise was observed in every instance irrespective of the findings in the clinical history concerning the precipitation of attacks in daily life by exertion. Other means of inducing angina (adrenalin<sup>4</sup> or anoxemia<sup>5</sup>) were tried in several instances but were unsatisfactory. The exercise, carried out according to the

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This investigation was aided by a grant from the DeLamar Mobile Research Fund.

method previously described," consisted of repeatedly mounting and descending a two-step staircase in a room maintained between 45 and 55° F. The exercise continued until the patient either developed a typical attack of angina pectoris or became fatigued without experiencing other discomfort.

If the patient developed angina pectoris, various observations were made *during the attack*. The actual duration of the pain was measured by stop watch. The areas to which distress was referred were determined by pointing in rapid succession to various parts of the chest, back, arms, etc., and asking whether pain was felt at that moment in that region. The patient was requested to describe the character of the discomfort. Both during and after the attack an attempt was made to learn in what respects the induced attack resembled or differed from those experienced in daily life. The accuracy of the findings was tested by repeating all observations in almost every patient.

#### RESULTS

The studies outlined above were made in 207 patients. The symptoms of 54 patients were apparently due to disease of the lungs, cervical or thoracic spine, esophagus, diaphragm, stomach, or gallbladder (Cases 1 to 11). The remaining 153 patients had angina pectoris. In two of these the attacks were precipitated by episodes of paroxysmal rapid heart action, one had thyrotoxicosis, one had marked secondary anemia, two had rheumatic heart disease, and two had syphilitic aortitis. The remaining patients (145) had angina pectoris presumably due to coronary artery disease. For simplicity of analysis, 100 consecutive patients in whom we were able to obtain all or most of the desired special studies were selected from the latter group. These 100 patients differed in no way from the entire group of 145 except for completeness of data.

#### *Sex, Age, Race, and Associated Diseases*

There were 77 men and 23 women; the characteristics of the disease were identical in both sexes.

The duration of the disease up to the time of study varied from five weeks to fifteen years. At the time of onset of the symptoms 65 per cent of the patients were between fifty and sixty-nine years of age. Five patients (3 men and 2 women) were under forty years of age (Table I).

Nine of the patients were non-Jewish. Race made no evident difference in the characteristics of the disease.

Thirty-seven patients had one or more attacks of coronary thrombosis; seven suffered from intermittent claudication of the legs; five had diabetes.

### History

*Symptomatology.*—One of the most characteristic features of the condition was the difficulty which patients experienced in describing the character of the discomfort. Questioning during an attack was frequently of distinct value. In all instances the sensation was described as disagreeable and uncomfortable, and in three-fourths of the patients as distinctly painful (Table II). The pain was obviously not as definite as that experienced in other conditions; in only six individuals was it sharp. Pressure or squeezing or their equivalents (heaviness, tightness) were frequent complaints, but patients agreed that these were inadequate descriptive terms.

TABLE I

THE AGE OF PATIENTS AT THE ONSET OF ANGINA PECTORIS

| AGE<br>(YEARS) | PER CENT OF<br>PATIENTS |
|----------------|-------------------------|
| 34-39          | 5                       |
| 40-44          | 12                      |
| 45-49          | 18                      |
| 50-54          | 29                      |
| 55-59          | 20                      |
| 60-64          | 13                      |
| 65-69          | 3                       |

TABLE II

THE SYMPTOMATOLOGY OF ANGINA PECTORIS

| SYMPTOM                      | PER CENT OF PATIENTS |
|------------------------------|----------------------|
| Pain                         | 76                   |
| Pressure (heaviness, weight) | 52                   |
| Dyspnea                      | 48                   |
| Squeezing (tightness)        | 33                   |
| Choking                      | 19                   |
| Palpitation                  | 11                   |
| Belching                     | 10                   |
| Burning                      | 4                    |

*Respiratory Symptoms:* Approximately half of our patients found it "hard to breathe" during attacks. Exactly what was meant by this expression was not always clear; in some instances it was apparently hyperpnea while in others it was a sensation of stifling. Patients who complained of shortness of breath usually showed an increased depth and rate of respiration during attacks induced by exertion, but similar respiratory symptoms were present when the attacks occurred at rest or were induced by excitement. Thirteen patients who denied shortness of breath showed definite and striking hyperpnea when observed during paroxysms.

*Palpitation* occurred in eleven patients. The occurrence of this symptom frequently made it difficult to determine whether the discomfort was characteristic of angina or was simply consciousness of the heart-

beat. Close questioning revealed that patients with angina pectoris experienced pain, pressure, or squeezing in addition to palpitation. Observation showed that the pain disappeared before the consciousness of the heart action subsided. The palpitation in this group was not associated with any abnormal rhythm and frequently continued after the heart rate had returned to normal.

*Belching* occurred in ten patients. In several instances termination of the attack and belching were almost simultaneous; in others belching occurred only while the patient was experiencing pain. Patients stated that, in association with the pain or squeezing, they experienced the sensation of a lump or a heaviness under the sternum which they felt would disappear on bringing up gas. It was obvious from observation that the belching followed the swallowing of air.

*Fear of impending death* was an infrequent and inconstant symptom. It was particularly experienced by hypersensitive, anxious patients, especially during the first few weeks or months after the onset or following an increase of symptoms. It frequently disappeared after a few attacks induced in the presence of a physician.

*The Onset of Attacks.*—In every instance the onset was sudden and required only a few seconds to reach its maximum intensity. The attacks usually came without warning, but occasional patients stated that unusual exertion or emotion might be attended by a premonition that an attack was about to develop.

*The Effect of Cold.*—Fifty per cent of eighty patients, who had observed the effect of temperature, noted that attacks were induced more readily by walking in the cold or against the wind. Five per cent developed pains more readily in warm weather. The remaining 45 per cent felt that temperature made little difference in the frequency of attacks. Direct observation has shown that the temperature of the environment is a very important factor in the case of inducing attacks.<sup>6</sup>

*The Effect of Food.*—We have not yet encountered patients who develop angina *solely* as a result of overeating. The usual story is that after heavy meals an attack is likely to be induced by less exertion than at other times (Table III). This has been demonstrated by actual

TABLE III  
CONDITIONS UNDER WHICH ATTACKS OF ANGINA WERE PRECIPITATED

| CONDITION    | PER CENT OF PATIENTS |
|--------------|----------------------|
| Exertion     | 100                  |
| Emotion      | 65                   |
| After meals  | 28                   |
| At rest      | 30                   |
| During sleep | 24                   |

observation.<sup>6</sup> One patient regularly developed tachycardia and angina following coffee; this was probably a response to caffeine.

*The precipitation of the attack by exertion* was an important diagnostic point (Table III). Two patients stated that attacks came only at rest and not on exertion; ten stated that attacks were usually induced by emotion but at times, or in the past, were precipitated by walking or climbing stairs. It was obvious from the clinical histories of these individuals that they rarely undertook any great degree of exertion. Regardless of the clinical history, *all* patients developed typical anginal attacks on exercise in the cold room except two individuals who had pain only in association with attacks of paroxysmal rapid heart action and one who had thyrotoxicosis.

*The Duration of Attacks.*—It was obvious that patients were unable to estimate accurately the duration of these paroxysms of discomfort. Half of the patients stated that the pain lasted either a few minutes or from five to ten minutes.<sup>7</sup> It is important to note that only four patients estimated that their attacks were *usually* fifteen minutes or longer in duration. Actual measurement of the duration of attacks indicated that they were practically always less than three minutes in duration.<sup>7</sup>

*Effect of Nitroglycerin in Terminating Attacks:* Eighty-two patients had tried this therapy. Forty-eight per cent believed that placing the tablet under the tongue shortened the attacks, 23 per cent were certain that it had been of no benefit; the remaining 29 per cent could not be certain whether or not it had made any difference. Patients without angina pectoris frequently reported relief from pain definitely non-cardiac in origin by using nitroglycerin (Case 9). Actual observation often failed to substantiate the patient's impression of the effect of nitroglycerin on the duration of attack.<sup>7</sup>

*Localization and Radiation of the Discomfort.*—There was considerable difficulty in describing the distribution of the discomfort unless patients were questioned while actually experiencing pain. So far as

TABLE IV  
LOCATION AND RADIATION OF DISCOMFORT DURING ANGINAL ATTACKS\*

| LOCATION              | ONSET OF<br>ATTACK<br>PER CENT OF<br>PATIENTS | SUBSEQUENT<br>INVOLVEMENT<br>PER CENT OF<br>PATIENTS | TOTAL<br>PER CENT<br>OF<br>PATIENTS |
|-----------------------|---|--|-------------------------------------|
| Substernal            | 74  | 9  | 83                                  |
| Left chest (anterior) | 21  | 13   | 34                                  |
| Apex of heart         | 6   | 2  |                                     |
| Axilla                | 0   | 3  |                                     |
| Shoulder (anteriorly) | 0   | 2  |                                     |
| Right chest           | 11  | 2  | 13                                  |
| Left arm              | 8   | 22   | 30                                  |
| Right arm             | 1   | 9  | 10                                  |
| Thoracic spine        | 16  | 5  | 21                                  |
| Epigastrium           | 6   | 2  | 8                                   |
| Throat                | 2   | 7  | 9                                   |
| Neck                  | 1   | 8  | 9                                   |
| Left side of head     | 0   | 1  | 1                                   |

\*In many patients pain occurred in several different areas simultaneously.



the patients could determine, identical areas were usually involved during the induced attacks and in those experienced in daily life; any slight difference was evident by comparison. Observation during attacks showed that all patients experienced discomfort in the anterior chest (Table IV). This roughly included an area between the anterior axillary lines, the lower costal border including the epigastrium, and the level of the first interspace including the suprasternal notch.

*The Distribution of Pain at the Onset of the Attack.*—In 89 per cent of the cases the discomfort began somewhere in the region outlined above. The substernal area (including about one inch to either side of the sternum) was by far the most common region to which the pain was referred; nevertheless, in one-fourth of the patients there was no substernal discomfort. The left chest was involved twice as often as the right. In six patients the pain began over the apex of the heart; in each of these instances the pain later radiated elsewhere in the anterior chest or the left arm. In eleven individuals the pain did not begin in the anterior chest; in three of these, the thoracic spine was the site of onset; in three, the epigastrium; in three, the left arm; in one, the right arm and in one the left lower jaw.

Pain in the shoulder proved to be either the anterior axillary fold or the region over the head of the humerus. Many patients experienced pain in the middle or upper thoracic spine, but this was rarely a prominent complaint and was elicited only by careful questioning during an attack. Only one patient had pain in the region of the scapula (left). With the exception of this patient and those who had pain in the spine, the posterior and lateral aspects of the thorax were free of discomfort.

*Radiation of the Discomfort.*—The description of the radiation of the discomfort often helped to clarify the diagnosis. The left arm and the left chest were the regions to which the pain radiated most frequently. It was often difficult for the patient to remember whether the inner or the outer aspect of the arm was affected but observation revealed that in every instance the inner aspect of the arm, i.e., the region of the biceps, the antecubital fossa, and the ulnar surface of the forearm, was involved. Two patients had pain along both the inner and outer surfaces of the arm.

In 56 per cent of the patients there was no radiation of the pain.

*The Frequency of Attacks.*—The majority of patients had one or more attacks each day, approximately 10 per cent had one attack or less each week (Table V). The frequency of attacks was of no value in diagnosis.

*Physical Examination.*—Physical examination was of little value in establishing the diagnosis of angina pectoris. The physical build of the patient was of some interest: sixty-one were stocky; thirteen were obese; the remaining twenty-six were definitely thin.

During attacks patients frequently developed an anxious expression and at times held both hands to the chest or clenched their fists as if to show that the sensation was one of squeezing or crushing. In some instances this aided in diagnosis. After the first or second induced attack, however, such patients usually lost their anxious expression and apparently were not uncomfortable.

*The Electrocardiogram, Blood Pressure, and Heart Size.*—It is evident that typical angina pectoris frequently occurs in patients with no abnormalities in heart size, blood pressure or electrocardiographic tracings (Table VI). One-half of the patients showed an entirely normal electrocardiographic tracing, the other half showed changes consistent with

TABLE V  
FREQUENCY OF ATTACKS IN 81 PATIENTS

|                   | PER CENT OF PATIENTS |
|-------------------|----------------------|
| About one a month | 7                    |
| About one a week  | 5                    |
| 2 to 6 a week     | 31                   |
| 1 to 2 a day      | 28                   |
| 2 to 5 a day      | 24                   |
| 5 or more daily   | 5                    |

TABLE VI  
THE ELECTROCARDIOGRAM, BLOOD PRESSURE, AND HEART SIZE IN ANGINA PECTORIS

|   | PER CENT OF PATIENTS |
|---|----------------------|
| Electrocardiographic evidence of coronary artery disease* | 50                   |
| Hypertension  | 44                   |
| Cardiac enlargement (x-ray)†                              | 25                   |
| Normal blood pressure, electrocardiogram, and heart size‡ | 26                   |

\*Studies made on 97 patients.

†Studies made on 74 patients.

‡Studies made on 70 patients.

coronary artery disease (slurring, spreading, or notching of the QRS complexes, elevation or depression of the S-T segment, inversion of T<sub>1</sub> or T<sub>2</sub>, upright T<sub>4</sub> or absent Q<sub>4</sub>). One patient had auricular fibrillation without decompensation. It must be remembered that similar electrocardiographic changes are seen in patients without angina pectoris.<sup>12</sup>

The blood pressure was measured in the right arm with the patient in the sitting position and was determined only once or twice on any given day. A more careful study with repeated measurements would undoubtedly yield a higher percentage of low blood pressure values. Hypertension (greater than 159 mm. Hg systolic or 99 mm. Hg diastolic) was found in slightly less than one-half the patients. Systolic pressures greater than 200 were rare. There was little demonstrable difference between the blood pressure readings of men and women. Two women with angina pectoris, each thirty-eight years of age, had blood pressures

of 112/58 and 112/80; in neither patient was there any evidence of pre-existing hypertension or coronary thrombosis.

Only one-fourth of the patients showed cardiac enlargement by x-ray examination.

Twenty-six per cent of all patients showed no abnormality in the electrocardiogram, blood pressure, or heart size by x-ray examination.

*The Basal Metabolic Rate and Serum Cholesterol Values.*—It has been suggested that low basal metabolic rates are relatively common in patients with angina pectoris,<sup>10</sup> but few figures are available. The basal metabolism of 40 per cent of our patients was between -11 and -25 per cent (Table VII). In no instance was there any clinical evidence of myxedema.

TABLE VII

THE BASAL METABOLIC RATE IN ANGINA PECTORIS (74 PATIENTS)

| BASAL METABOLIC<br>RATE | PER CENT OF<br>PATIENTS |
|-------------------------|-------------------------|
| +11                     | 4                       |
| ± 0 to +10              | 24                      |
| ± 0 to -10              | 32                      |
| -11 to -15              | 18                      |
| -16 to -25              | 22                      |

TABLE VIII

SERUM CHOLESTEROL VALUES IN ANGINA PECTORIS (68 PATIENTS)

| SERUM CHOLESTEROL<br>MG. PER 100 C.C. | PER CENT OF<br>PATIENTS |
|---------------------------------------|-------------------------|
| 150-199                               | 10                      |
| 200-249                               | 31                      |
| 250-299                               | 43                      |
| 300-349                               | 10                      |
| 350-399                               | 4                       |
| 400-413                               | 2                       |

Approximately 60 per cent had an increased cholesterol content of the blood (Table VIII). In general, a low basal metabolic rate was accompanied by an elevation of the serum cholesterol, but high cholesterol values were also found in individuals with normal metabolic rates.

*Angina Pectoris Associated With Other Forms of Heart Disease, Anemia, or Thyrotoxicosis.*—The character, the location, and the radiation of the discomfort were the same in all cases of angina pectoris regardless of whether the underlying pathology was coronary arteriosclerosis or some other condition which might induce myocardial anoxemia. In patients with other forms of heart disease, however, attacks were frequently more severe, longer in duration, and more likely to come on at rest or during sleep than in uncomplicated Heberden's angina.

We were unable to induce attacks by exercise in two patients whose attacks occurred only during episodes of paroxysmal rapid heart action (auricular fibrillation or auricular tachycardia). These patients stated

that the palpitation usually came while at rest and the pain began shortly after the onset of the rapid heart action and disappeared shortly after the cessation of the arrhythmia.

Attacks indistinguishable from uncomplicated Heberden's angina were induced in two patients with rheumatic and two with syphilitic aortic disease. Four other patients with aortic disease were not included in the present series of 207, for it was considered inadvisable to have them exercise. The clinical histories of two with aortic stenosis (one of rheumatic, the other apparently of arteriosclerotic origin) differed in no way from the 100 analyzed above. The other two had aortic regurgitation of rheumatic origin. Attacks of angina were ushered in by an increase in heart rate and systolic blood pressure while at rest, on motion in bed, or during meals. The characteristics of these attacks were similar to those secondary to paroxysms of abnormal rhythm.

One patient with anemia differed in no way from the hundred cases analyzed above. Correction of the anemia resulted in an increase in the amount of work which could be done before developing angina but did not entirely prevent attacks. One patient with thyrotoxicosis has been reported previously.<sup>6</sup> We were unable to induce attacks of angina in this patient by exertion; thyroidectomy has resulted in improvement but not "cure" of the angina.

#### COMMENT

The majority of patients with Heberden's angina are persons of stocky or "vascular" build; men are more commonly affected than women; the ages forty-five to sixty-five years are most frequent and from one- to two-thirds of patients show abnormalities in the electrocardiogram, blood pressure, heart size, basal metabolic rate or serum cholesterol level. The clinical history may reveal that the attacks are associated with a fear of impending death or that the pain can be terminated by nitroglycerin. In individual instances, however, these findings are of no specific diagnostic value.

The first and most important step in diagnosis is to obtain an adequate description of the symptomatology. In our experience all patients with angina pectoris showed five diagnostic characteristics in common:

1. *Onset* sudden, in "attacks."
2. *Duration* short, usually more than a few seconds but less than "fifteen minutes."
3. *Symptoms* difficult to describe; pain, pressure, squeezing, choking, or their equivalents.
4. *Region involved*, the anterior chest (including the epigastrium) and the inner aspect of the arms (especially the left). Radiation of the discomfort is important, if it occurs.
5. *Attacks precipitated by exertion*, especially climbing stairs or walking in the cold.

Patients who lacked one or more of these five features proved to have either noncardiac disease as the cause of their symptoms or angina pectoris plus some complicating disease.

The history as volunteered by the patient must be analyzed and evaluated to determine its reliability, accuracy, and completeness. Additional questioning is frequently necessary to obtain adequate information concerning the five diagnostic points. Certain variations are frequently met and deserve comment; in most instances the disagreement is apparent rather than actual.

*Onset and Duration.*—An occasional patient has prolonged attacks or constant pain. Such individuals, however, may recognize episodes of sudden exacerbation of symptoms which have all the characteristics of anginal attacks. The constant pain in such instances is frequently a comparatively mild soreness or hyperesthesia of the skin or bone which persists for hours or days after the acute paroxysm has subsided.

An *occasional* attack of long duration does not rule out angina pectoris; in fact many patients pass through a period of comparatively prolonged and more severe attacks.<sup>9</sup> The significance of these is not clear. In some instances careful study may prove the episode to be due to coronary thrombosis; in other instances fever, leucocytosis, and electrocardiographic changes may be absent, but an elevation in sedimentation rate may occur, suggesting myocardial damage.<sup>8</sup> Patients whose attacks always last longer than one-half hour usually prove to have no cardiac disease as the cause of the prolonged attacks (Cases 6 and 10).

*The characterization of the discomfort* will vary with the experience and vocabulary of the patient. An owner of real estate described "the Empire State Building pressing" on his chest; a retired cowboy felt "a lariat about the throat." The one characteristic in common is a vague unrest or distress difficult to describe.

*The region affected* is best determined by having the patient point specifically to the area where he experiences pain during attacks. This may be difficult and observation during attacks may reveal an entirely different area of involvement. Discomfort experienced in the posterior or lateral aspects of the thorax (except the region of the dorsal spine), the outer aspects of the arms or the shoulders, or the abdomen should make one suspicious and search for a noncardiac explanation of all or part of the picture (Cases 8 to 11).

*Precipitation of Attacks by Exertion.*—The occurrence of attacks during rest or sleep and the effect of emotion is well known. In an occasional patient these aspects may be so prominent that the precipitation by exertion may be overlooked. Patients whose attacks *never* come on exertion are rare and are usually those who take but little exercise. Such patients may have had attacks on effort in the past; in many instances this association of pain and exertion has been the cause of the

limitation of activity. It is frequently helpful to ask such patients what would happen if they were to run up stairs.

The apparent variation in the amount of work which patients can perform from day to day before developing pain argues against exertion as an important factor. These variations, however, are due to changes in the temperature of the environment; the emotional state of the individual; the amount of food recently eaten; physiological changes occurring after attacks which make successive paroxysms either more or less easily precipitated; and, at times, to actual variations in the course of the disease. When patients exercise under standardized conditions, the amount of work which can be done before inducing an attack is extraordinarily constant.<sup>6</sup>

The terms "angina of effort," "angina of rest," and "angina of emotion" are probably misnomers. So far as can be determined, these are simply different conditions under which the same symptom-complexes may be precipitated. It is more logical and satisfactory to speak of "angina *on* exertion," "angina *on* emotion," and "angina *during* rest or *during* sleep."

Angina pectoris secondary to valvular heart disease, aortitis, paroxysmal arrhythmias, anemia, or thyrotoxicosis was quite similar to that due to coronary artery disease, but the attacks were likely to be more prolonged and frequently occurred without obvious precipitating cause. The frequency of patients with such complicating features varies in different parts of the world. It is apparent, however, that they constitute a comparatively small proportion of the large group of patients who suffer from angina pectoris and that they rarely offer any great problem in diagnosis.

Difficulties in diagnosis are usually due to one of four reasons: first, the symptoms may suggest a noncardiac disorder. This is especially true if the discomfort begins in an unusual area, such as the epigastrium, arms, or jaw, or if other symptoms, such as belching, apparent relief by soda, or attacks following meals are a prominent part of the picture (Cases 1 to 4). Second, noncardiac disease may suggest angina. It must be remembered that precordial distress may be caused by pathological processes in the cervical or thoracic spine, lungs, diaphragm, esophagus, stomach or gallbladder (Cases 5 to 9). Third, the patient may have angina pectoris in addition to noncardiac disease. Under such conditions the anginal distress may be hopelessly interwoven with other complaints, making it impossible for even the most experienced examiner to be certain in his appraisal of the situation (Cases 10 and 11). Fourth, in many instances language difficulty, emotional instability, inadequate observation, or the vagueness of symptoms makes it impossible for the patient to present a clear picture of his sensations.

The standardized exercise tolerance test enables one to obtain specific information concerning four of the five important diagnostic points: the

ability to induce paroxysms by exertion, the speed of onset of attacks, the duration of symptoms, and the location of the discomfort. Additional information concerning the character of the discomfort can also be obtained at times by questioning the patient during an attack. In our experience, observation of the response to exertion has resulted in a change in diagnosis and treatment in many instances while in others important information not available from the clinical history was obtained.

The test is not infallible, but its accuracy is apparently great. Out of 207 patients tested, we have had reason to doubt the result in but six. Two patients who failed to develop discomfort on exertion suffered coronary thrombosis several months after being tested. The clinical histories did not warrant a definite diagnosis of angina pectoris in these individuals, but it is possible that they did have angina and were tested during a remission. One patient who developed pain on exertion died of carcinoma of the esophagus; no autopsy was performed, but it was felt that this patient had coronary arteriosclerosis. The two patients with angina secondary to paroxysmal rapid heart action and the one with thyrotoxicosis have been commented on.

It is neither necessary nor advisable to resort to an exercise or work test in every instance. Many patients are capable of describing their symptoms in a manner which leaves little to be desired, while adroit questioning of others will yield sufficient information concerning the important diagnostic criteria. We must never lose sight of the fact that angina pectoris is a serious condition, and coronary thrombosis or sudden death may come without warning. While it would appear that little danger is involved in a patient's undertaking, in the presence of a physician, exertion similar to that which he performs frequently in daily life, nevertheless, one should refrain from exercising patients whose symptoms are unusually severe, or those who experience "weakness" on exertion.

It is to be expected that errors will occur when the diagnosis rests solely on the patient's ability to describe his symptoms. The frequency of error decreases, however, as the examiner becomes more experienced and as attention is paid not only to the story as volunteered by the patient but also to the important diagnostic criteria above enumerated. There will remain, undoubtedly, a group of patients in whom it is impossible to be certain of the diagnosis from the history alone; the diagnosis in such patients can usually be made by observation during attacks, if necessary, precipitated by exertion.

#### SUMMARY AND CONCLUSIONS

1. Approximately two hundred patients suspected of suffering from angina pectoris have been studied in order to establish the criteria for diagnosis and to determine the frequency of atypical forms of the syn-

drome. The studies include a careful evaluation of the clinical history, physical examination, electrocardiographic tracings, teleroentgenograms of the heart, the basal metabolic rate, the blood serum cholesterol, and the patient's reaction to exercise under standardized conditions.

2. Five characteristics were of importance in the diagnosis of angina pectoris: the attacks were sudden in onset, short in duration, involved the anterior chest (including the epigastrium) and inner aspect of the arms, were induced by exertion in the cold, and consisted of a vague sensation of unrest or distress difficult to describe. Patients who lacked one or more of these features proved to have either no cardiac disorder as the cause of their symptoms or to have angina pectoris plus some complicating disease.

3. There were other characteristics which were encountered frequently but which were of no specific diagnostic value in any individual instance. These included abnormalities in the electrocardiogram, blood pressure, heart size, basal metabolic rate, serum cholesterol level, and the relief by nitroglycerin. Twenty-six per cent of all patients with angina showed no abnormalities in the electrocardiogram, blood pressure, or heart size by x-ray examination.

4. Angina pectoris due to valvular heart disease, paroxysmal rapid heart action, anemia, or thyrotoxicosis was quite similar to that secondary to coronary artery disease, but the attacks were likely to be prolonged and frequently occurred without obvious precipitating cause.

5. Difficulties in diagnosis were usually due to noncardiac disease simulating angina pectoris, angina pectoris simulating noncardiac disease, angina pectoris and noncardiac disease occurring together in the same individual, or inability of the patient to present a clear picture of his sensations.

6. Observation of the patient's reaction to exercise was frequently of distinct value in establishing the diagnosis or obtaining a more exact picture of the symptoms than was possible from the clinical history alone.

#### REFERENCES

1. Heberden, W.: Commentaries, Med. Trans. Coll. Physicians, London 2: 59, 1768.
2. Aub, J. E., and Du Bois, E. F.: Clinical Calorimetry, Arch. Int. Med. 19: 823, 1917.
3. Ling, S. M.: The Determination of Cholesterol in Small Amounts of Blood, J. Biol. Chem. 76: 361, 1928.
4. Levine, S. A., Ernstene, A. C., and Jacobson, B. M.: The Use of Epinephrine as a Diagnostic Test for Angina Pectoris, Arch. Int. Med. 45: 191, 1930.
5. Rothschild, M. A., and Kissin, M.: Production of the Anginal Syndrome by Induced General Anoxemia, AM. HEART J. 8: 729, 1933.
6. Riseman, J. E. F., and Stern, B.: A Standardized Exercise Tolerance Test for Patients With Angina Pectoris on Exertion, Am. J. M. Sc. 188: 646, 1934.
7. Riseman, J. E. F., and Brown, M. G.: Duration of Attacks of Angina Pectoris and the Effect of Nitroglycerine and Amyl Nitrite. New England J. Med. (in press).
8. Riseman, J. E. F., and Brown, M. G.: The Sedimentation Rate in Angina Pectoris and Coronary Thrombosis, Am. J. M. Sc. In press.



9. Riseman, J. E. F., and Brown, M. G.: The Clinical Course of Angina Pectoris. In preparation.
10. Libman, E.: Personal communication.
11. Hanflig, S. S.: Pain in the Shoulder Girdle, Arm and Precordium Due to Cervical Arthritis, J. A. M. A. 106: 523, 1936.
12. Barnes, A. R.: Electrocardiogram in Myocardial Infarction, Arch. Int. Med. 53: 455, 1935.
13. Lynn, T. A., and Horgan, E.: Dissection of the Thyroid from the Sympathetic Nervous System and Reduction of the Blood Supply to the Thyroid in Angina Pectoris, South. M. J. 12: 985, 1934.

### CASE REPORTS

#### CASE 1.—*Angina Pectoris Simulating Gastrointestinal Disease.*

Mr. M. S., an instrument worker, had been in good health until the age of forty-two years, when he first noticed "a dull cramp" in the region of the epigastrium, which came on exertion, such as swimming. This lasted only a "few moments" and disappeared on rest. X-ray films of the gastrointestinal tract revealed no pathology. A diagnosis of "nervous indigestion" was made.

Two and one-half years later the patient noted that in addition to the epigastric discomfort there was a sense of choking and pain in the suprasternal notch, which, at times, radiated to the left arm. The attacks were only a few minutes in duration and disappeared on rest. A diagnosis of angina pectoris was made, and medical therapy was instituted but without improvement. A year and one-half later he was referred to the Beth Israel Hospital for total thyroidectomy.

Physical examination revealed no abnormalities. The patient was well nourished, short and stocky. The heart was of normal size by x-ray examination; blood pressure, 145/85; electrocardiogram showed left axis deviation, inverted  $T_1$  and  $T_2$ . Basal metabolic rate was -8 per cent. Exercise in the cold room precipitated, after fifty-eight trips, an attack which was similar in all respects to those which he had had on the outside and was undoubtedly angina pectoris.

*Comment.*—Pain limited to the epigastrium suggested that this patient's symptomatology was due to a gastrointestinal disorder and only when discomfort radiated to the suprasternal notch and the left arm was it possible to make a definite diagnosis of angina pectoris. The precipitation of epigastric discomfort by exercise, the short duration of the symptoms, the relief by rest, and the lack of relationship to food, should have raised the suspicion that the condition might be cardiac rather than gastric.

#### CASE 2.—*Angina Pectoris Simulating Gastrointestinal Disease.*

Mr. P. S., aged forty years, a dry goods salesman, stated that three weeks before entering the hospital, while walking to work in the morning, he suddenly experienced pressure under the sternum which forced him to stop in order to catch his breath. There was no radiation of the pain, but it was accompanied by a feeling of choking and an intense desire to belch. The attack lasted about "two minutes" and left him feeling quite well. Since that time he had had five to six similar attacks, usually occurring while walking to work in the morning. On one occasion he took a Seidlitz powder with prompt relief.

Physical examination was essentially negative except for tenderness to palpation over the right costal margin. The blood pressure was 130/92. X-ray examination revealed no cardiac enlargement. Electrocardiographic tracings were normal except for prominent  $Q_1$  and  $Q_2$ . Oral cholecystogram revealed normal filling and emptying. Blood serum cholesterol was 298 mg. per 100 c.c. Basal metabolic rate was -10 per cent.

*Comment.*—The history in this case is apparently quite similar to that of Case No. 5. Both patients were forty years of age. The attacks

had been noticed for only a few weeks. The discomfort in both instances was in the substernal region, was associated by a desire to belch, and was relieved by Seidlitz powder or bicarbonate of soda. Careful questioning, however, revealed important differences in the duration of the attacks and the relationship to food and exertion. The relief by seidlitz powder, in this case, was not real, for the attacks continued for several minutes after taking the powder, whereas other attacks not so treated were no more prolonged. After twenty-two trips in the cold room the patient developed an attack of angina pectoris which was typical of the attacks that he experienced on the outside. A month after discharge, the patient developed a coronary occlusion, from which he recovered.

CASE 3.—*Angina Pectoris Simulating Neuritis.*

Mrs. R. K., a housewife, was well until the age of forty-five years. At this time a panhysterectomy was performed, following which she developed vague aches and pains in various parts of her body. Her blood was found to show a slight increase in the number of white cells and the smear contained 50 per cent lymphocytes, all of which were normal. There was no glandular enlargement and no evidence of blood disease. Two years later she developed attacks of pain beginning in the left wrist and radiating up the left arm to the substernal region and to the apex of the heart. These were usually precipitated by exertion especially in the cold; excitement also induced attacks, and occasionally they awakened her at night. The pain she stated was of "a pressing, squeezing character as if the sleeve had become too tight." She was unable to tell whether the sensation was on the inner or outer aspect of her arm. With the pain she felt very short of breath. The attacks came on once or twice a week, and were frequently accompanied by belching.

Physical examination was entirely negative. The heart was not found enlarged by x-ray; blood pressure was 160/90. Electrocardiogram was normal except for left axis deviation. Basal metabolism was +3 per cent. Serum cholesterol was 269 mg. per 100 c.c.

*Comment.*—The patient believed she was suffering from indigestion, for belching accompanied the attacks. The pain in the arm, however, led to a diagnosis of neuritis, and she was treated accordingly for several months. Exercise in the cold room induced a typical attack of angina pectoris which began after 32 to 38 trips. The pain began on the flexor surface of the wrist, radiated up the inner aspect of the arm, and finally reached the midsternal region. The attack lasted one and one-half minutes and subsided first in the chest, then in the arm and finally in the wrist. For a period of approximately a year this patient was treated with various forms of medicinal therapy without any striking improvement. She died suddenly during sleep.

CASE 4.—*Angina Pectoris Simulating Dental Pathology.*

Mr. H. C., aged fifty-two years, a retired tailor, had been well, except for mild diabetes, until about two months before admission, when he began to complain of discomfort in the left lower jaw severe enough to force him to stop walking. This pain usually began as pain in the region of a capped tooth. If he persisted in walking, he felt a choking sensation in the throat, a squeezing sensation in the retrosternal region, and pain along the inner aspects of both arms. With the attacks he frequently broke out into a sweat. The paroxysms usually lasted "10 to 15 minutes."

Physical examination revealed a short obese individual in whom the left lower canine tooth served as one anchor for a bridge, and the cap had worn away at the base exposing the tooth. The blood pressure was 140/70. X-ray film of the heart showed slight enlargement to the left. Electrocardiogram showed low T-waves in all leads, inverted T<sub>2</sub>, absent Q<sub>2</sub>, M-shaped QRS<sub>2</sub>. The urine showed no sugar; blood sugar was 123 mg. per 100 c.c. The basal metabolism was -19 per cent.

Ten months after the onset of symptoms, a denervation of the thyroid, according to the method of Lyon and Horgan,<sup>13</sup> was performed; this was followed by relief of pain in the chest and the right arm. He continues to have pain in the jaw and left arm on exertion and excitement.

*Comment.*—The patient was quite certain that the pain was due to his teeth. X-ray films revealed alveolar recession but no other pathology. It was inconceivable that dental pain should be induced by exertion and should spread to the neck, the chest, and the arms. Exercise in the cold room precipitated an attack after ten trips which was similar to that described by the patient. About two months later the duration and frequency of the attacks increased. The electrocardiogram at that time showed inversion of T<sub>2</sub> and T<sub>3</sub>.

*CASE 5.—Gastrointestinal Disease Simulating Angina Pectoris.*

Mr. M. G. (35476A), aged forty years, complained of a sense of "pressure or heaviness" under the sternum, which came on while walking and after meals, did not radiate, and was occasionally relieved by belching.

Physical examination was essentially negative except for a blood pressure of 165/100, palpable and thickened brachial and radial vessels, the dorsalis pedis pulsation was absent.

*Comment.*—Angina pectoris was suspected, and the response to exertion was studied. No attack was precipitated by one hundred trips under the standardized conditions of the test. Further questioning revealed that the discomfort usually came on after his noonday meal, at which time he usually walked about the streets during his lunch hour; the symptoms also occurred after other meals, while at rest. The distress usually continued for approximately a half hour, was not aggravated by continued walking. Nitroglycerin gave no relief, but sodium bicarbonate gave immediate relief. It was obvious that this was not a case of angina pectoris but was more likely due to disturbed function of the gastrointestinal tract. The discomfort disappeared on a gastric regime.

*CASE 6.—Gallbladder Disease Simulating Angina Pectoris.*

Mr. J. S. had been previously examined in two other hospitals where diagnoses of arteriosclerotic heart disease, coronary thrombosis (old), and angina pectoris had been made. For three years before admission to the Beth Israel Hospital he had experienced attacks of severe, squeezing pain in the chest coming on once or twice a day, usually while resting quietly, frequently following meals. They were rarely induced by exertion, but the patient had been living a very inactive life. These attacks usually lasted from fifteen minutes to one or two hours, were unrelieved by nitroglycerin, and often required morphine for relief. On at least two occasions the attacks had been so severe that several weeks' rest in bed had been prescribed.

Physical examination revealed a hyperactive, short, stocky man. The left pupil was irregular and smaller than the right. There was peripheral arteriosclerosis. The blood pressure was 170/90.

Examination of the urine and blood revealed no abnormal findings. The blood Wassermann reaction was negative. Serum cholesterol was 280. Basal metabolic rate -2 per cent. The heart was not enlarged by roentgenogram; electrocardiographic tracings showed left axis deviation and a deep  $S_2$ . During the patient's stay in the hospital the symptoms disappeared entirely, and, after three weeks, he was discharged with diagnoses of hypertensive and arteriosclerotic heart disease, angina pectoris, pulmonary emphysema.

Six weeks later he returned with a story that ten days before reentry, while sitting quietly in a chair, he experienced an attack of squeezing in the midsternal region which lasted for two hours and required hypodermic medication for relief. This pain was preceded by profuse sweating. During the next few days he had several similar but less prolonged attacks. Examination at this time revealed essentially the same findings as at the previous admission. Repeat electrocardiographic tracings showed an inverted  $T_3$ , which later became upright.

*Comment.*—The history in this patient was consistent with angina pectoris. Certain features, such as the prolonged duration of the attacks and the onset during rest and following meals rather than on exertion, made it advisable to investigate further. X-ray films of the gastrointestinal tract revealed no pathology. Cholecystograms by both the oral and intravenous method revealed no gallbladder shadow. A roentgenogram of the cervical spine showed hypertrophic changes at the anterior and posterior margins of the cervical vertebrae.

Because of the apparent severity of symptoms the patient's response to exercise was studied with great caution. The first test was stopped after he did a relatively small amount of work (ten trips), and on each subsequent test the amount of work which he was allowed to do was increased. On the fourth test he made sixty-two trips in three and one-half minutes. This resulted in moderate dyspnea and fatigue of the legs but no precordial distress.

If this patient suffered from angina pectoris in as severe a form as was apparent from the history, it would have been impossible for him to have done this amount of work. Accordingly, he was discharged with instructions to take a low-fat, high carbohydrate diet, small meals, and tincture of belladonna after meals. There has been no recurrence of the symptoms during the ten months since discharge. This is the longest period that he has been free of discomfort for three years.

*CASE 7.—Pathology of the Esophagus Simulating Angina Pectoris.*

W. D., a physician, aged thirty-seven years, while running up two flights of stairs two steps at a time, developed a sharp, choking pain under the middle of the sternum. There was no radiation of this discomfort, and after resting for "a second or so" it disappeared. Following this episode, he experienced the pain many times a day, frequently with exertion, and frequently while resting quietly. Physical examination was negative. Electrocardiogram was normal.

*Comment.*—The momentary nature of the discomfort, together with the fact that it came on just as frequently while at rest as during exer-

tion, made it seem unlikely that the symptoms were cardiac in origin. The patient's age, the character of the discomfort and the lack of radiation were also somewhat against this diagnosis. The patient, however, thought that it might be angina, for five years previously, while pushing an automobile in the cold after taking two or three cocktails, he had developed auricular fibrillation which lasted several hours.

He requested to be allowed to "exercise in the cold room." Four weeks after the onset of the symptoms he performed fifty trips (equal to approximately five flights of stairs) without any discomfort; he was told that he did not have angina pectoris. A few weeks later he noticed that the pain came on chiefly when swallowing, especially saliva. X-ray examination revealed esophagitis and two small diverticuli about the middle third of the esophagus on the posterior surface. The patient's symptoms disappeared entirely following a modified Sippy regime.

CASE 8.—*Arthritis Simulating Angina Pectoris.*

Mrs. S. S., aged fifty-six years, stated that for six months she had been experiencing a needlelike and burning pain in the chest radiating down the left shoulder and left arm. This pain usually came while walking, was most commonly felt during cold weather, was associated with shortness of breath and disappeared a few minutes after she stopped and rested. In addition, she had pain and stiffness of the fingers of both hands.

Physical examination was essentially negative. The blood pressure was 160/80, and there was slight cyanosis of the lips.

*Comment.*—The clinical history suggested angina pectoris as the most likely cause of the symptoms. On observation during exertion, it was evident that the pain was experienced in the region of the fifth and sixth interspaces *between the anterior and posterior axillary lines* on the left and also on the *posterior aspect of the left arm*. It was also evident that this pain came not on exertion but on motion. Bending of the trunk was sufficient to induce the pain in the chest, while bending of the head brought on the pain in the shoulder and the left arm.

It was evident that this patient did not have angina pectoris. The pain was due to pathology in the spine, similar in character to the atrophic arthritis in the hand.

CASE 9.\*—*Arthritis Simulating Angina Pectoris.*

Mr. H. T., aged fifty-four years, had been troubled by pain in the chest radiating to the outer aspect of both arms for about two years. The discomfort usually came on at night while in bed and woke him from sleep. It was unassociated by shortness of breath or sweating and was never induced by walking or climbing stairs. The attacks usually occurred several times a week, lasted from a few seconds to ten or fifteen minutes. A physician prescribed nitroglycerin which gave him considerable relief, and at one time an operation was advised for relief of this heart pain.

Physical examination revealed moderate arteriosclerosis, the heart size was shown to be within normal limits by x-ray examination; the electrocardiogram was normal.

*Comment.*—This was apparently a case of angina pectoris, but exercise in the cold room failed to produce any precordial discomfort. Sub-

\*This case has been reported previously by Dr. S. Hanslg.

cutaneous injection of adrenalin induced a rise in blood pressure and a severe pain above the left breast, radiating to the left shoulder down the arm to the elbow. This was not relieved by lactose tablets but was relieved by nitroglycerin. This attack was in all likelihood angina pectoris, but the attacks which he experienced in daily life were different in character. X-ray films of the cervical and the dorsal spine revealed slight lippling about the anterior margins of the fourth and fifth cervical vertebrae. Motion of the head brought out pain in the affected regions. It seemed evident that the patient was suffering not from angina pectoris but radiculitis due to arthritis of the cervical spine. The apparent relief by nitroglycerin was seemingly against this diagnosis, but it was soon found that tablets of lactose under the tongue gave as rapid relief as did nitroglycerin.

The cervical spine was stretched and manipulated according to the method outlined elsewhere,<sup>11</sup> with complete but temporary relief from the symptoms. Repeated orthopedic treatment has been necessary on several occasions during the past few years. The patient has at times shown evidences of arthritis in the left shoulder and both hands.

CASE 10.—*Angina Pectoris and Cholelithiasis.*

Mrs. D. K., a forty-two-year-old housewife, was admitted to the hospital because of "indigestion." Eighteen years ago, she had a fainting spell, following which she developed a burning pain in the right upper quadrant which radiated to the region of the right shoulder blade. For three or four days she vomited frequently and required morphine for relief of the pain. During the next year the discomfort returned at frequent intervals and prevented her from working. Thirteen years ago she experienced belching and distress in the upper abdomen for several weeks. On one occasion she fainted. A diagnosis of gastric ulcer was made. Operation revealed no gastric lesion, but a pathological gallbladder was drained, following which treatment she was free from discomfort for some time. Nine years ago she developed nausea and an "annoying, dull, tearing" pain in the right upper quadrant which was accentuated by exertion and relieved by rest. X-ray studies revealed adhesions in the region of the gallbladder and duodenum. Operation was refused. Four months ago she again developed cramping, nagging pains in the right upper quadrant, coming on about three hours after meals, and accompanied by a sensation of pressure under the heart which took her breath away. At times these pains would radiate to the left shoulder and down the left arm.

Physical examination was essentially negative. The patient was well developed, short, and stocky. The blood pressure was 120/80. The blood and urine were normal; serum cholesterol, 291; electrocardiogram revealed flat T<sub>1</sub> and low T<sub>2</sub>. Oral cholecystogram revealed a faint gallbladder shadow with a calcified stone in the fundus.

*Comment.*—The history was consistent with gallbladder disease except for the radiation to the left shoulder and left arm. Careful questioning revealed that the patient really had two types of discomfort—pain and distention in the epigastrium and right upper quadrant which usually lasted for hours and which she had had off and on for years; and pain and pressure in the region of the cardiac apex, at times radiating to the left shoulder and arm, which would last about five minutes

and which she had had for about four months. These latter attacks came on at times following the prolonged pain in the right upper quadrant, and they also came with exertion and emotion when the right upper quadrant pain was absent. The patient naturally believed that all these symptoms were due to her gallbladder and only by careful questioning as to the duration, character, and mode of onset was it possible to separate the two groups of symptoms.

After forty trips over the two-step staircase in the cold room, the patient developed a sense of pressure over the region of the cardiac apex, which did not radiate and which continued for about forty-five seconds after stopping the exercise. This sensation was typical of some of the less severe attacks which she had experienced at home and was entirely different from the symptoms in the right upper quadrant.

A diagnosis of cholelithiasis and angina pectoris was made. The patient was operated upon, and a diseased gallbladder was removed.

Reexamination a year later revealed that the pain in the right upper quadrant had disappeared following the operation, but the pain in the chest and left arm had become more frequent. It was precipitated by walking, emotion, and coughing. Exercise in the cold room again precipitated an attack of angina pectoris which radiated to the inner aspect of the left arm and was similar in all respects to that which she experienced when at home.

CASE 11.—*Angina Pectoris Associated With Diaphragmatic Hernia and Morphine Sensitivity.*

Mrs. B. B., a fifty-two-year-old housewife, had had hypertension for twenty-five years, nocturia, occasional dizzy spells, spots before the eyes, ringing in the ears, and severe headaches for ten years. Thirteen years ago her gallbladder was removed. Beginning nine years ago, she began to experience sudden severe attacks of precordial pain brought on by exertion or "aggravation" or following a heavy meal. These usually lasted about five to ten minutes and were frequently accompanied by nausea and vomiting. On three of four occasions these attacks had been very severe, were associated with a fall in blood pressure, required injections of morphine for relief, and were treated by prolonged rest in bed. For many years she had had swelling of the ankles toward evening, and on several occasions during the past three years had been awakened from sleep by shortness of breath.

Physical examination revealed the patient to be obese. There were moderate cardiac enlargement and a soft systolic murmur at the aortic area. The blood pressure was 190/100. The liver was palpable two fingerbreadths below the costal margin. There was minimal pitting edema of the legs. The lungs showed râles at both bases. The urine and blood were normal; serum cholesterol was 378 mg. per 100 c.c.; basal metabolic rate, -20 per cent. X-ray examination of the chest revealed calcification of the aorta. Electrocardiographic tracing showed deep  $S_2$ , inverted  $T_2$ , elevated  $S-T_2$ , with late inversion.

The excitement of coming to the hospital precipitated a severe attack of precordial pain for which she was given morphine. Shortly thereafter she vomited, the pain returned and morphine was again administered. Vomiting continued for several days, and the vomitus and stools revealed occult blood. When morphine was discontinued, the vomiting soon ceased.

*Comment.*—It was evident that the patient had hypertensive and arteriosclerotic heart disease with angina pectoris and mild congestive failure. The atypical feature was the frequent occurrence of vomiting with the attacks of heart pain. Exercise in the cold room precipitated an attack of precordial pain similar to that experienced at home but not accompanied by vomiting. X-ray films of the gastrointestinal tract revealed a diaphragmatic hernia.

The vomiting was apparently due to the diaphragmatic hernia and sensitivity to morphine. Severe attacks of angina were frequently treated by morphine, which in turn caused vomiting. The discomfort of nausea and vomiting would frequently precipitate other attacks of angina. As a result, the patient was unable to differentiate between the different two groups of symptoms.



## UNUSUAL CLINICAL MANIFESTATIONS OF SUBACUTE BACTERIAL ENDOCARDITIS\*

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THE three cases here reported are given in some detail because of their unusual clinical interest. In one, pericarditis was present at the same time as subacute bacterial endocarditis, bringing up the moot question of the relationship between active rheumatic infection and subacute bacterial endocarditis. Post-mortem examination showed that the pericarditis was due to a perforation of a mycotic aneurysm of the sinus of Valsalva with extension of the infection to the pericardium and that it was not due to active rheumatic involvement. In the second, a triad of rare findings occurred in the same patient—auricular fibrillation before the onset of the bacterial endocarditis, polycythemia, and a spleen which was not palpable at any time during the course of the disease. The third was admitted to the genito-urinary service for perinephritic abscess, but was in reality a case of subacute bacterial endocarditis with splenic infarction. When the infarct became infected the patient developed a subphrenic abscess with perforation of the diaphragm and left-sided empyema.

CASE 1.—I. S., a male, aged twenty years, student, was admitted Aug. 16, 1936 because of cough and substernal oppression for several days. The patient had migratory polyarthritis in 1926 and rheumatic endocarditis in 1929 (when mitral stenosis, mitral insufficiency, and aortic insufficiency were diagnosed). In 1933 he suffered a recurrent attack of endocarditis. He was well enough between his periods of illness to lead an active life. Two weeks before his present admission he complained of a stiff neck and a fever of 102° F. He later developed a slightly productive cough and a sensation of pressure over the precordium for two days before admission.

*Physical Examination.*—The patient appeared acutely ill, cyanotic; temperature was 103.6; pulse, 126; respirations, 34. The head bobbed with each heart beat. The neck showed no tracheal deviation or tug. Lungs: There were diminished breathing, dullness and râles at the left base; other areas were normal. Heart: The heart was markedly enlarged to the left. A double aortic murmur was heard at the base and a blowing systolic with an early diastolic murmur (probably transmitted from the base) could be heard in the mitral area. The rhythm was regular, the rate, 125. Blood pressure was 120/0. The abdomen was negative; no edema was present, no petechiae, and only slight clubbing of the fingertips.

*Laboratory Findings.*—Repeated specimens of urine showed specific gravity up to 1.024 with a rare granular cast, and an occasional faint trace of albumin. A few red blood cells were found in 4 of 24 specimens (during the first week of his stay).

The blood never showed a true anemia (5,580,000 red blood cells with 98 per cent hemoglobin on admission; 4,180,000 red blood cells with 80 per cent hemoglobin

\*From the Medical Service of the Beth Israel Hospital.

three days before death). The white blood count varied between 8,350 and 13,600; the sedimentation rate between 45 mm. and 23 mm. fall in forty-five minutes. The venous pressure was 2 cm. Blood culture showed between 2 and 75 colonies of *Streptococcus viridans* per cubic centimeter. Pericardial fluid on September 12 and October 2 showed no organisms and no growth on culture. Blood Wassermann reaction was negative; blood chemistry normal.

*Electrocardiogram* (August 17) showed right axis deviation with slurring and notching of QRS in Leads I and III, suggesting myocardial damage.

*Roentgenogram* (August 28) showed marked accentuation of the ascending aorta and the left ventricular contour; no accentuation of left auricular or pulmonary conus. The apex extended to within a short distance of the axillary line. The cardiac silhouette was that of an aortic lesion, predominantly aortic insufficiency. There was no evidence of pericardial effusion.

*Course.*—It was felt on admission that the patient might be suffering from recurrent rheumatic carditis, particularly in view of typical Ewart's breathing at the left base posteriorly, probably due to pericarditis with effusion. At the same time blood cultures continued to show *Streptococcus viridans* in increasing number, definitely establishing the case as one of subacute bacterial endocarditis. The patient soon began to show signs of diffuse embolization (petechiae, etc.).

The bronchial breathing at the left base became more and more marked so that a diagnostic pericardial tap was performed (September 12), which yielded 30 c.c. of straw-colored fluid. The culture of this fluid was negative, the cell count 430 per cubic centimeter with 90 per cent polymorphonuclears and 10 per cent lymphocytes. Although this did not change the signs at the left base, a distinct pericardial friction rub was audible over the sternum the next day. The patient at this time developed a patch of bronchopneumonia in the right middle lobe. He began to show signs of peripheral collapse and circulatory failure. On September 21 there was marked costovertebral tenderness, probably due to renal infarcts. Three days later he had an episode of abdominal pain and rigidity in the left upper quadrant, interpreted as indicating splenic infarction. The spleen, however, was not palpable at any time, even though there was exquisite tenderness in the left upper quadrant. The area of dullness and bronchial breathing in the left chest posteriorly now began to reach a higher level. On the second pericardial tap (October 2) 150 c.c. of serous fluid were removed; this showed 420 cells per cubic centimeter, 73 per cent polymorphonuclears, 27 per cent lymphocytes, specific gravity 1.008. A loud friction rub was heard anteriorly after the pericardial tap. Gallop rhythm superseded the normal. The patient died on October 10, 1936, about eight weeks after admission.

#### AUTOPSY REPORT (DR. A. PLAUT)

*Diagnosis.*—Old and recent aortic endocarditis with valvular aneurysm and insufficiency of the aortic ostium. Mitral endocarditis with insufficiency of the ostium. Acute pericarditis. Dilatation and hypertrophy of heart, notably of left ventricle. Infarcts in spleen and kidney.

*Heart.*—The heart weighed 980 gm. On the anterior left ventricular surface was an area 2 cm. in diameter with a number of small, light yellowish-gray, friable tags adherent to the surface. The heart was enormously dilated and hypertrophied, especially on the left. The right auricle and ventricle were dilated. The pulmonary ring was widened; otherwise the valve appeared normal. The mitral ring was 17 cm. in circumference. The chordae tendineae were extremely long, thickened, and fused together. Some of the chordae contained minute, grayish-pink, verrucous vegetations; a row of small verrucae lay along the closure line of the valve. The aortic ring was greatly widened, the valves were thickened and fused along the com-

missures. They bore large, hard, rough, gray, vegetations. There was an aneurysm of the sinus of Valsalva of the posterior aortic cusp. The myocardium was moderately firm, pale purplish. No focal lesions were found. The left ventricular wall was 20 mm. thick, the right, 5 mm. The coronaries were wide and thin-walled. Directly below the aortic ring an indistinctly outlined, partly calcific, partly soft yellow area, 1.5 cm. in diameter, was seen. The *aorta* was quite elastic and contained many small atheromatous plaques in the ascending and thoracic portions about the openings of the vessels. *Microscopically*: No rheumatic lesions were found in the heart. The inflammatory lesions were uncharacteristic. The subepicardial fat tissue was infiltrated with small round cells. Small and large foci of granulation tissue were found scattered throughout the myocardium. The valvular lesions consisted of accumulations of leucocytes, fibrinoid necrosis of connective tissue, and some proliferation of endothelial cells and fibroblasts. The abscess-like focus below the aortic ring contained calcific material and uncharacteristic inflammation. There was moderate diffuse fatty change in the myocardium.

*Lungs*.—The lungs appeared edematous and hyperemic. The pleura was smooth and glistening.

*Spleen*.—The spleen weighed 300 gm., and was large and firm. It contained infarcts and recent infarct scars.

*Kidneys*.—The left kidney weighed 180 gm., the right, 160 gm. The capsule, cortex, and medulla appeared normal. There were several depressed scars due to fresh infarcts. Microscopically no Loehlein lesion or other important glomerular lesion was found.

*Pelvic Organs*.—*Suprarenal*; *Stomach*, and *Intestines* were normal. The *Liver*; stasis with poor definition of the acinar structure due to central atrophy.

#### DISCUSSION

The autopsy confirmed the clinical diagnosis of pericarditis, but this was evidently due to extension of the infective process from the mycotic aneurysm of the sinus of Valsalva to the pericardium and not to active rheumatic infection, as the absence of Aschoff bodies at post-mortem examination showed. It must be admitted that the pericarditis was interpreted clinically as probably due to recurrent rheumatic infection and not to the relatively rare condition that the autopsy revealed. It should be stressed here that this cause for pericarditis in a patient with bacterial endocarditis is not as rare as we formerly believed. Dr. Klemperer\* demonstrated the organs of a case of subacute bacterial endocarditis very similar to our own. The patient, a man of fifty-three years, had clinical evidence of pericardial effusion, aortic disease, and subacute bacterial endocarditis. At autopsy no Aschoff bodies were found, but an acute pericarditis was present due to a mycotic aneurysm of the sinus of Valsalva that had penetrated deep down and involved the pericardium. Dr. Klemperer recalled two more cases that had severe ulcerating lesions of the aortic valve giving rise to pericarditis. We must think then of this lesion when we find frank signs of pericarditis in a case of subacute bacterial endocarditis not showing any manifestations of active rheumatic infection.

\*Mount Sinai Hospital Pathological Conference Oct. 24, 1936. Case No. 10,096.

It is important to note that if no autopsy had been performed in this case the final clinical diagnosis would in all probability have been rheumatic pericarditis (i.e., an active rheumatic infection) in the presence of subacute bacterial endocarditis. We believe that this is an infrequent occurrence clinically, although there have been many references to the closer association of these two conditions.<sup>1, 2, 3</sup> The stand that the usual subacute bacterial endocarditis is implanted on recently active rheumatic lesions and not on the basis of old or healed rheumatic valvular lesions has lately been taken very effectively by von Glahn and Pappenheimer.<sup>4</sup> In 26 consecutive patients with subacute bacterial endocarditis (of all ages) which they report, 46 per cent showed Aschoff bodies post mortem. This is about the same proportion as in uncomplicated rheumatic carditis.<sup>2c</sup> We do not know from the article whether these subacute bacterial cases gave clinical as well as pathological evidence of rheumatic activity. It appears as if pathologically the two conditions occur with greater frequency than they are suspected clinically, possibly because the presence of subacute bacterial endocarditis overshadows the clinical manifestations of active rheumatic endocarditis. It is interesting to note that in the case here reported the situation was exactly the reverse, the presence of pericarditis was interpreted as indicative of active rheumatic infection, while pathologically the evidence for active involvement of the heart was absent. Perhaps it may be said, as Saphir and Wile<sup>3</sup> have shown, that in the younger age groups bacterial endocarditis is often engrafted on a fresh endocarditis. In the older age groups, and where a long period of time separates the known rheumatic infection and the advent of bacterial endocarditis, it is more likely that the bacterial endocarditis is implanted on a *chronically* injured valve. From the clinical point of view, however, it is not common to find frank clinical evidence of active rheumatism in a case of subacute bacterial endocarditis, and even the presence of pericarditis is not necessarily indicative of active rheumatic involvement of the heart in a case of subacute endocarditis.

It should be noted finally that there was not at any time evidence of anemia in this case of subacute bacterial endocarditis. On admission the red blood count was 5,580,000 with 98 per cent hemoglobin; and 4,180,000 with 80 per cent hemoglobin terminally. This was not due to dehydration or increased concentration of blood. Case 2, also failed to show anemia until the very last few weeks.

CASE 2.—J. R., male, aged thirty-five years. The patient had pancarditis in 1917, and recurrent fever the following year. He thought he had made a complete recovery, and felt well until four days before his first admission (Feb. 16, 1936) when he complained of low-grade fever, weakness, and general malaise. At this time he had an enlarged heart and auricular fibrillation. Laboratory: red blood cells numbered 7,080,000 with hemoglobin 110 per cent. White blood count was 8,600 with 74 per cent polymorphonuclears and 3 per cent macrophages. Sedimentation rate 14 mm. fall in 45 minutes. There were no red blood cells in the urine. Blood culture

showed 24 colonies of *Streptococcus viridans*. There were no other clinical manifestations of subacute bacterial endocarditis, such as embolization or petechiae. The five months' interval between admissions was spent mainly in bed because of persistent fever, cough, and weakness. During this entire period there were no skin lesions, weight loss, or night sweats. He was readmitted July 22, 1936 because of chest pain of three days' duration.

*Physical Examination.*—On readmission the patient appeared chronically ill, but well nourished. Temperature was 101° F.; pulse, 120; respirations, 26. There was no clubbing of the fingers; no petechiae. The heart was enlarged to the left. Auricular fibrillation was present with no pulse deficit. Systolic and diastolic murmurs were heard at the apex. The lungs were negative. The spleen and liver were not palpable.

*Laboratory Findings.*—A typical urine specimen (February 22) showed specific gravity 1.020; albumin, faint trace; 4 to 6 red blood cells and 3 to 4 white blood cells per high-power field; occasional hyaline cast; red blood cells were present in 8 of 12 urine specimens examined. The red blood count had fallen from the previous admission to 4,370,000 with 73 per cent hemoglobin on July 22. Shortly before death (September 13) the red blood count was only 3,420,000 with 65 per cent hemoglobin. There were 12,450 white blood cells, 83 per cent polymorphonuclears and 2 per cent macrophages. Sedimentation rate (July 23) 52 mm. in 45 minutes. Blood culture on 4 occasions showed 100 to 300 colonies per cubic centimeter. Blood Wassermann reaction was negative, blood chemistry, normal.

*Electrocardiogram* (July 23) showed auricular fibrillation. On August 24 an electrocardiogram showed frequent ventricular premature contractions in addition.

*Roentgenogram* at the bedside (July 31) showed the cardiac contour to be that of double mitral valvular lesion. There was a diminution in aeration in the lower half of the left lung field, but no definite evidence of infiltration or consolidation of the lungs.

*Course.*—The day after admission (July 23) petechiae appeared on the soft palate, which lasted forty-eight hours. Several days later he had extreme pain in the lower left chest radiating to the left shoulder, heralding infarction of the spleen. Soon after this the patient complained of abdominal pain and distention, probably due to embolization of some intestinal vessel. On August 21 there was a recurrence of pain in the left lower chest made worse by deep inspiration, suggestive of fresh splenic infarction. On September 5 edema of both ankles, a tender, distended liver, and a marked pulse deficit appeared. With active digitalization the cardiac failure was cleared somewhat. On September 11, however, pain in the lower left chest recurred and a definite friction rub could be heard over the spleen, due to a perisplenitis. Râles appeared at both bases, and respiratory difficulty rapidly increased. The patient died on September 19, two months after his re-admission. No autopsy was done.

#### DISCUSSION

On the first admission the patient demonstrated several findings that are unusual for subacute bacterial endocarditis. These were the poly-*cythemia* (7,080,000 red blood cells with 110 per cent hemoglobin), the presence of auricular fibrillation, the absence of a palpable spleen. To come across such a triad in a case of bacterial endocarditis is rare indeed and made us doubt the diagnosis until the further clinical course justified it.

On the second admission (July 22) the red blood count was 4,370,000 with 73 per cent hemoglobin. This should be considered a relative anemia and a marked fall in the red blood cells when compared with the original counts in February, 1936. Towards the last weeks of the patient's life the blood showed a true anemia, as might be expected in a case of bacterial endocarditis (3,420,000 red blood cells with 65 per cent hemoglobin).

The presence of auricular fibrillation at the beginning of the clinical manifestations of subacute bacterial endocarditis is rare indeed. It is a good practical dictum, stressed by many clinicians,<sup>1, 5-8</sup> that a fibrillator is spared the advent of a complicating bacterial endocarditis. Sprague<sup>9</sup> reports an interesting case which disproves this rule, as do de la Chapelle and Graef.<sup>10</sup> In Segal's<sup>11</sup> review of 192 cases of bacterial endocarditis three instances of auricular fibrillation were described. In only one, however (Case 3), was the fibrillation present before the development of the subacute bacterial endocarditis, and this is the only case that resembles our own. In the others the fibrillation occurred for a short period towards the end of the disease.

The absence of a palpable spleen throughout the clinical course of the disease in this patient is to be noted. Although Blumer<sup>5</sup> in his excellent review of the literature says an enlarged spleen was present in only 74 per cent of the cases, he was speaking mainly of single examinations. On the wards of Beth Israel Hospital we have been able, in the great majority of cases to palpate an enlarged spleen at some time during the disease; surely in more than 90 per cent. Unfortunately an autopsy was not permitted in this patient so that we do not have definite knowledge about the size of the spleen. Note, however, that the spleen was not palpable in Case 1 of this report, and here autopsy showed an enlarged, infarcted, spleen. It is likely that the same thing occurred in this second case—that repeated infarctions with concomitant perisplenitis made the spleen less movable on deep inspiration, so that it could not be palpated.

**CASE 3.**—B. M., a male milliner, aged twenty-five years, was admitted, Nov. 6, 1934, to the genito-urinary service because of sudden severe sticking pain in the left flank radiating to the left costal border four weeks before admission, followed by fever rising to about 102° F. at night. Anorexia and weight loss (35 lb. in four weeks) developed. One week before admission the patient voided reddish urine frequently for several days.

*Physical Examination.*—The patient appeared acutely ill and emaciated. Temperature was 105° F.; pulse, 110; respirations, 30. Lungs were negative. The heart was slightly enlarged to the left. A high-pitched diastolic murmur was heard in the aortic area transmitted to the left border of the sternum as far as the apex. The blood pressure was 145/65. There was rigidity and tenderness in the left flank as far as the costovertebral angle.

*Laboratory Findings.*—A typical urine specimen (November 6) showed specific gravity 1.025, albumin faint trace; 10 to 20 red blood cells, and 6 to 8 white blood

cells per high-power field; no casts. The blood showed (November 6) 4,000,000 red blood cells, 85 per cent hemoglobin, white blood cells 12,000 with 79 per cent polymorphonuclears. This rose to 44,000 with 96 per cent polymorphonuclears on November 19 when empyema developed. Blood smear from the ear lobe (November 17) showed 3 per cent macrophages. Blood cultures (November 17 and 19) were sterile. Urine culture was negative for tubercle bacillus colonies. Blood Wassermann reaction was negative. Blood chemistry showed nonprotein nitrogen 66 on November 7, and 31 on November 12.

*Electrocardiogram* (November 21) showed sinus tachycardia with low amplitude T<sub>1</sub> and T<sub>2</sub>, suggesting myocardial damage.

*Röntgenogram of the chest* (November 16) showed effusion in the lower portion of the left pleural cavity with deviation of heart to the right. There was exaggeration of the right and left cardiac contours.

*Course.*—From the history, it was believed at first that the patient was suffering from a perinephritic abscess. Cystoscopy revealed turbid urine in both ureters with many red blood cells and white blood cells. The concentrating power was not impaired, however. Pyelographic examination of the urinary tract was entirely negative, showing no evidence of perinephritic abscess or urinary calculus. The patient continued to run fever for a week. On medical consultation, signs of frank pleurisy at the left base were found. In addition to the aortic diastolic murmur a mitral systolic and diastolic were now heard. The edge of the spleen was palpable. It was considered that the presence of fever, a palpable spleen, and hematuria in a case of valvular heart disease (aortic) pointed strongly to the diagnosis of subacute bacterial endocarditis. The effusion in the chest following a bout of pain in the left flank suggested a splenic infarct with subsequent suppuration which had extended to the left pleural cavity. The blood culture was negative; but there were 3 per cent macrophages on blood smear. The signs of fluid in the left chest increased and aspiration revealed a sanguino-purulent fluid. On rib resection the left diaphragm was found very high. While exploring the empyema cavity an opening was made through the softened diaphragm into a pocket of subdiaphragmatic pus. The exact location of this pus could not be determined because of the precarious condition of the patient. Following operation the patient continued to do poorly in spite of blood transfusion. He finally succumbed six days after operation; about three weeks after admission.

#### AUTOPSY REPORT (DR. A. PLAUT)

*Diagnosis.*—Empyema of left pleural cavity. Perforation of left dome of diaphragm leading into broken-down splenic infarct. Perisplenic adhesions. Aortic endocarditis with insufficiency. Circumscribed mitral endocarditis with formation of so-called valvular aneurysm. Dilatation and hypertrophy of left ventricle. Kidney infarct. Glomerulonephritis, partly of the embolic bacterial type, partly true Loehlein lesion.

*Heart.*—The heart weighed 323 gm. The left ventricle was wider than normal. One centimeter above the free edge of the mitral commissure a very soft, hyperemic mass 1.5 cm. in diameter protruded, attached to the valve by a broad base. There were soft, purplish-gray vegetations on the ventral surface of the valve. A small hole in the center formed a so-called valvular aneurysm. The aortic leaflets were the seat of an old endocarditis. They were shortened and thickened; the free edges had a moth-eaten appearance and had fine reddish masses upon them. One centimeter below the base of the right cusp there were irregularly crescent-shaped thickenings in the endocardium of the septum. The ascending aorta was slightly atheromatous, otherwise normal. The inside of the sinus of Valsalva showed nothing remarkable. The coronary arteries were wide and normal. The auricles, the pulmonary and

tricuspid valves, and the myocardium of the right side showed nothing abnormal. *Microscopic:* The section from the aortic valve does not show recent endocarditis. Crushed smear from vegetation of heart valve shows numerous gram-positive streptococci in chains of 4 to 6.

*Lungs.*—Bronchi, arteries, and lung tissue were normal, except for slight emphysema.

The spleen, pancreas, stomach, and the left dome of the diaphragm formed a large, irregular soft mass. At the highest point of the left dome of the diaphragm there was a rough circular opening about 7 cm. in diameter leading into an irregular cavity with torn bloody walls, and irregularly torn splenic tissue. It was separated from the diaphragm by fat tissue. Smaller infarct-like areas were seen at different points. Fibrin-like masses could be seen when the adherent diaphragm was partly removed from the surface of the spleen. An abscess the size of a small almond was situated within the diaphragm. The liver, which weighed 2,040 gm., was hyperemic and showed some fatty changes.

*Kidneys.*—The kidneys were large, and stripped easily from the capsules. The left kidney contained a yellow, roughly wedge-shaped nonprotruding corpus with a hyperemic marginal zone. *Microscopic:* The yellow focus was an infarct. The glomerular pictures varied considerably. Some glomeruli were almost normal, some showed the capsular changes of glomerulonephritis, while other glomeruli gave a characteristic picture of a Loehlein lesion.

#### DISCUSSION

There are several points of interest in this case. The initial reference of the patient to the genito-urinary service rather than the medical is not an infrequent occurrence when the presenting symptoms are high intermittent fever and hematuria. We have seen this error made several times before. The diagnosis of subacute bacterial endocarditis could not be confirmed ante mortem in this patient because the blood culture was sterile. The differential diagnosis was mainly between perinephritic abscess and splenic infarction with secondary infection in a case of subacute bacterial endocarditis. Aside from the negative pyelographic findings and the positive findings in the heart, several other considerations pointed to the latter diagnosis. Elevation of the diaphragm is not common in perinephritic abscess, while it is the rule in subphrenic. The pain in the left upper quadrant radiating to the left costal margin pointed to a perisplenitis such as one sees in infarction rather than a kidney lesion. Splenic infarction is likely to occur terminally and not as the early clinical manifestation of subacute bacterial endocarditis that this case showed. From the history it appears that the splenic infarction occurred during the first month and that the patient did not die directly from the subacute bacterial endocarditis but rather from a complication of the disease—a secondary infection of a splenic infarct. There was frank pus in the splenic abscess which was evidently due to a secondary infection, for the *Streptococcus viridans* (recovered from the heart valves) is not a pus-producing organism and could not in itself have been responsible for the pus found in the spleen, diaphragm and left pleural cavity.



## SUMMARY AND CONCLUSIONS

Three clinically unusual cases of subacute bacterial endocarditis are reported. In one a pericarditis was present concomitantly with subacute bacterial endocarditis. The pericarditis was clinically believed to be a manifestation of active rheumatic infection—at autopsy it was found to be due to an extension of infection from a mycotic aneurysm of the sinus of Valsalva to the pericardium. This cause for pericarditis in a patient with subacute bacterial endocarditis is not as uncommon as formerly believed. The question of the relationship between active rheumatic infection and subacute bacterial endocarditis is discussed. Their simultaneous presence occurs oftener in children apparently than in adults.

The second case is one in which auricular fibrillation preceded the subacute bacterial endocarditis and persisted throughout its course. This is contrary to the clinical dictum which has been considered almost axiomatic—that fibrillation spares the patient subacute bacterial endocarditis. The case also failed to demonstrate a palpable spleen throughout the entire course of the illness, even though there was clinical evidence of repeated splenic infarctions. When the subacute bacterial endocarditis was first detected in this patient he had a secondary polycythemia (7,080,000 red blood cells with 110 per cent hemoglobin). For fully five months of the illness he suffered a relative, but not an absolute anemia. The combination of three such rare findings as fibrillation, a nonpalpable spleen and a polycythemia in a patient with subacute bacterial endocarditis is considered worth noting.

In the third case which was mistaken at first for perinephritic abscess because of intermittent fever and hematuria, autopsy showed that the patient had bacterial endocarditis and a splenic infarct which had become secondarily infected. The abscess broke through the diaphragm and caused a fatal empyema. The cardiac murmurs, palpable spleen, and the subphrenic involvement pointed to the correct diagnosis.

The authors are deeply indebted to Dr. Isidore W. Held for his invaluable aid in the clinical observations of these patients.

## REFERENCES

1. Libman, E.: (a) The Clinical Features of Subacute Streptococcus (and Influenzal) Endocarditis in the Bacterial Stage, *M. Clin. North America* 2: 117, 1918.  
Libman, E.: (b) Characterization of Various Forms of Endocarditis, *J. A. M. A.* 80: 813, 1923.  
Libman, E.: (c) Discussion of paper by Saphir and Wile, *AM. HEART J.* 9: 109, 1933.
2. Clawson, B. J., Bell, E. T., and Hartzell, T. B.: (a) Valvular Disease of the Heart With Special Reference to the Pathogenesis of Old Valvular Defects, *Am. J. Path.* 2: 193, 1926.  
Clawson, B. J., and Bell, E. T.: (b) A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis, *Arch. Int. Med.* 37: 66, 1926.  
Clawson, B. J.: (c) The Aschoff Nodule, *Arch. Path.* 8: 664, 1929.

3. Saphir, O., and Wile, S. A.: Rheumatic Manifestations in Subacute Bacterial Endocarditis in Children, *AM. HEART J.* 9: 29, 1933.
4. Von Glahn, W. C., and Pappenheimer, A. M.: Relationship Between Rheumatic and Subacute Bacterial Endocarditis, *Arch. Int. Med.* 55: 173, 1935.
5. Blumer, G.: Subacute Bacterial Endocarditis, *Medicine* 2: 105, 1923.
6. Thayer, W. S.: Studies on Bacterial (Infective) Endocarditis; Introductory Remarks and General Considerations, *Johns Hopkins Hosp. Rep.* 22: 1, 1926.
7. Horder, T.: Lumelien Lectures on Endocarditis, *Lancet* 1: 695 (also 745 and 850), 1926.
8. Rothschild, M. A., Sachs, B., and Libman, E.: The Disturbance of the Cardiac Mechanism in Subacute Bacterial Endocarditis and Rheumatic Fever, *AM. HEART J.* 2: 356, 1927.
9. Sprague, H. B.: Subacute Bacterial Endocarditis; A Correlation of the Clinical Evidence of Valvular Deformity With the Condition of the Valves as Found at Autopsy, *J. A. M. A.* 94: 1037, 1930.
10. de la Chapelle, C. E., and Graef, I.: Occurrence of Subacute Bacterial Endocarditis in Mitral Valvular Disease With Preexisting Auricular Fibrillation, A Case Report, *AM. HEART J.* 8: 352, 1932.
11. Segal, M. S.: (a) Auricular Fibrillation and Auricular Flutter in the Course of Subacute Bacterial Endocarditis, *New England J. Med.* 212: 1077, 1935.  
Segal, M. S.: (b) Bacterial Endocarditis With Special Reference to the Cardiac Irregularities, *AM. HEART J.* 11: 309, 1936.

# SUBACUTE BACTERIAL ENDOCARDITIS

## CLINICOPATHOLOGICAL STUDY OF THIRTY-SEVEN CASES\*

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**S**UBACUTE bacterial endocarditis continues to be one of the most dreaded diseases, especially to that group of patients who have a mild chronic rheumatic lesion of the heart and who would otherwise enjoy several years of fairly good health. Davis and Weiss<sup>1</sup> have estimated that about one of every ten patients having rheumatic heart disease will acquire subacute bacterial endocarditis. Thus, it is possible to see what a menace it is to this particular group. Thirty-seven cases of subacute bacterial endocarditis in which necropsy was performed form the basis of this report.

*Age and Sex.*—The decade of greatest incidence varies in different series of cases. Clawson<sup>2</sup> found about an equal incidence in the third, fourth, and fifth decades of life. Davis and Weiss observed that in the largest number of their cases the patients had acquired the disease in the fifth decade, while Fulton and Levine<sup>3</sup> found that the disease most frequently occurred in the third decade of life. In twelve (32 per cent) of the thirty-seven cases which form the basis of this report, the patients had acquired the disease in the fourth decade of life, and in the remainder of the cases the age of the patients varied; the youngest patient was ten years and the oldest was sixty-seven years of age.

Rheumatic heart disease is more prevalent among females than it is among males. It, therefore, would seem logical to expect that the incidence of subacute bacterial endocarditis also would be more prevalent among females. This, however, has not been true in other series of cases which have been reported in the literature. Nor was it true in the

TABLE I  
INCIDENCE ACCORDING TO AGE AND SEX

| PATIENTS   |       |         |
|------------|-------|---------|
| AGE, YEARS | MALES | FEMALES |
| -1 to 9    | 0     | 0       |
| 10 to 19   | 1     | 3       |
| 20 to 29   | 4     | 3       |
| 30 to 39   | 9     | 3       |
| 40 to 49   | 4     | 2       |
| 50 to 59   | 2     | 0       |
| 60 to 69   | 5     | 1       |
| Total      | 25    | 12      |

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series of cases which we have observed, as twenty-five of the patients were males and twelve were females; in other words, the ratio of males to females was approximately 2 to 1 (Table I).

*Bacteriology.*—The *Streptococcus mitior* (*Streptococcus viridans*) is the most common etiologic agent. In twenty-nine cases the blood culture yielded a growth of *Streptococcus mitior*; in five cases the blood culture did not reveal any growth; and in the remaining three cases the cultures yielded *Diplococcus pneumoniae*, type I, *Diplococcus pneumoniae*, type II, and *Proteus ammoniae*, respectively.

*Other Laboratory Data.*—The Wassermann reaction on the blood serum was positive in four cases, but necropsy in these cases failed to disclose any syphilitic lesion of the heart or aorta, on which a subacute bacterial endocarditis might have been superimposed.

The erythrocyte count in all cases except three was materially reduced at the time the patients were first examined at the clinic. In twenty of the thirty-seven cases the number of erythrocytes ranged between 3,000,000 and 4,000,000 per cubic millimeter of blood. In the remainder, except the three cases mentioned previously, the number of erythrocytes was less than 3,000,000 per cubic millimeter of blood. The number of leucocytes varied from 2,600 to 38,000 per cubic millimeter of blood. Leucopenia has been reported frequently, but because most of the patients in this series of cases were seen in the later stages of the disease, this finding was not noted frequently. In twenty-six of the cases the value for the hemoglobin was less than 10 gm. (60 per cent) per 100 c.c. of blood.

The specimens of urine in all cases contained some albumin, but in nine cases no erythrocytes could be found in the urine.

In eight cases the value for urea was 60 mg. or more per 100 c.c. of blood. In four of these cases death was the result of a complicating uremia; in those cases values for the urea were 411, 273, 314, and 268 mg. per 100 c.c. of blood, respectively. The renal function remains good in most cases, even though an embolic nephritis is present.<sup>2</sup>

*Duration of Symptoms.*—The insidious onset of the disease makes it difficult for most patients to tell exactly when the illness began. The total duration (from onset of symptoms to time of death) of symptoms in no case was longer than one year and in thirty cases (80 per cent) it was six months or less.

*Embolic Manifestations.*—Nineteen (51 per cent) patients of this group had clinical manifestations of emboli in one or more forms. Fifteen had petechiae of the skin, conjunctiva, or mucous membranes of the mouth. Five patients had hemiplegia which was the result of cerebral emboli. In seven cases petechial hemorrhages were present in the retina. One patient died of an intraperitoneal hemorrhage which was caused by a rupture of a mycotic aneurysm of the splenic artery.

*Splenic Enlargement.*—The idea is common that the spleen should be palpable in cases of subacute bacterial endocarditis. In twenty-four cases (64 per cent) the spleen was not definitely palpable. In only two cases of the entire group was the spleen not enlarged (200 gm. or more) at necropsy. The average weight of the spleens which were not palpable was 402 gm., while the average weight of those which could be palpated was 478 gm. Thus, in most cases the spleen was enlarged even though it was not palpable. Infarcts, recent or ancient, were present in the spleen in all cases except one.

*Relationship of Chronic Valvulitis to Subacute Bacterial Endocarditis.*—In nineteen (51 per cent) of the cases there was a history of rheumatic fever. In five of these cases there was no good pathological evidence of a rheumatic endocarditis. In the remaining group of eighteen cases there were seven in which there was a chronic valvulitis. Twenty-two (60 per cent) of the patients had chronic valvulitis which was indicative of a previous infection. Three had the subacute process superimposed on calcified aortic valves. The ages of these three patients were sixty-seven, sixty, and sixty-six years, respectively. The etiology of this calcareous lesion of the aortic valves was not clear. This leaves twelve cases (32 per cent) in which there was no pathological evidence of a previous valvulitis on which the subacute process might have been engrafted.

*Degree of Underlying Valvular Deformity in Relation to Subacute Bacterial Endocarditis.*—Sprague<sup>4</sup> reviewed the post-mortem and clinical findings in twenty cases of subacute bacterial endocarditis in which the mitral valve was involved and found that in none of the cases was the circumference of the valve less than 8 cm. Clinical examination revealed that only one patient had mitral stenosis (loud first sound with a presystolic murmur) and that all the others had a mitral regurgitation (loud systolic murmur). The degree of rheumatic valvular damage in forty-seven cases of subacute bacterial endocarditis studied by Davis and Weiss corresponded with that which was found in 474 cases of rheumatic valvulitis. These authors said that the mild rheumatic lesions are not involved more frequently (in percentage) than advanced rheumatic lesions since they are much more frequent. In this series of cases the mitral valve was involved by the subacute process in twenty-seven cases; in twenty of these cases there was an underlying chronic valvulitis. The average circumference of the mitral valve in these twenty-seven cases was 10 cm. In only four of these cases was the circumference of the mitral valve less than 8 cm., the measurements being 6.5 cm., 7.0 cm., 7.0 cm., and 6.0 cm., respectively. The electrocardiogram also gave some corroborative evidence. An electrocardiogram was made in thirteen of the cases of mitral subacute endocarditis and in only one of these cases was there a right axis deviation (right ventricular preponderance). Necropsy in this case revealed a mitral

valve which measured only 6 cm. in circumference. None of the electrocardiograms revealed an auricular fibrillation, which usually comes on after a stenosis of the mitral valve has been present for some time. It is not important to determine if the mild rheumatic lesions are involved more frequently (by percentage) than the stenotic lesions, but it is important to realize that subacute bacterial endocarditis shortens the lives of those who have rheumatic endocarditis and who would otherwise enjoy several years of fairly good health.

*Endocardial Involvement.*—The idea is somewhat prevalent that in cases of subacute bacterial endocarditis the aortic valve is attacked more frequently than is the mitral valve. This has not been true in this series. Clawson and Bell<sup>5</sup> have also found that the ratio of involvement of the mitral and aortic valves is about the same in subacute bacterial endocarditis as it is in chronic valvulitis. In this series of cases the mitral valve was the only one involved in seventeen (46 per cent) cases and the aortic was the only one involved in ten (27 per cent) cases. Both the mitral and aortic valves were attacked in eight (21.6 per cent) cases; the mitral, aortic and tricuspid valves were involved in one case; and the mitral and tricuspid valves were involved in one case.

The post-mortem appearance of the heart in a typical case was as follows: The heart weighed 390 gm. and was of a pale brown color. The consistency was normal and the incised surface was the same color as the pericardial surface. There was not any streaking of the myocardium. The foramen ovale was closed, and there was no evidence of coronary sclerosis. The mitral valve was the site of old endothelial thickening and the chordae tendineae of the mitral valve were short and thick. There were fresh vegetations on the chordae tendineae and along the edge of the mitral valve; these extended upward into the anterior and medial wall of the left auricle. These were pinkish, rounded cauliflower-like growths. The aortic valve measured 6 cm., and the mitral valve measured 10 cm. in circumference.

*Weight of the Heart.*—The weight of the heart varied from 222 gm. to 800 gm. When compared with the computed weights, as determined by the normal body weight according to the method of Smith,<sup>6</sup> the hearts were found to be enlarged in all except three cases. As would be expected, the largest hearts were found in those cases in which there was an aortic endocarditis.

#### SUMMARY

In this series subacute bacterial endocarditis was more common among males than among females. In the majority of cases the patients were in the third, fourth, and fifth decades of life. Embolic processes were common. The spleen was almost invariably enlarged, even though not palpable. The *Streptococcus mitior* was the usual etiological agent but

it was not the only one. A rheumatic infection commonly precedes subacute bacterial endocarditis. The degree of previous valvular damage is usually mild. The mitral valve is involved more frequently than is any other valve. In no case was the duration of symptoms more than one year and in 80 per cent of cases it was six months or less.

## REFERENCES

1. Davis, David, and Weiss, Soma: The Relation of Subacute and Acute Bacterial Endocarditis to Rheumatic Endocarditis: A Study of 66 Cases With Necropsies, *New England J. Med.* 208: 619, 1933.
2. Clawson, B. J.: An Analysis of 220 Cases of Endocarditis With Special Reference to the Subacute Bacterial Type, *Arch. Int. Med.* 33: 157, 1924.
3. Fulton, M. N., and Levine, S. A.: Subacute Bacterial Endocarditis With Special Reference to the Valvular Lesions and Previous History, *Am. J. M. Sc.* 183: 60, 1932.
4. Sprague, H. B.: Subacute Bacterial Endocarditis: A Correlation of the Clinical Evidence of Valvular Deformity With the Condition of the Valves as Found at Autopsy, *J. A. M. A.* 94: 1037, 1930.
5. Clawson, B. J., and Bell, E. T.: A Comparison of Acute Rheumatic and Subacute Bacterial Endocarditis, *Arch. Int. Med.* 37: 66, 1926.
6. Smith, H. L.: The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, *Am. Heart J.* 4: 79, 1928.

## Department of Clinical Reports

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### THE OCCURRENCE OF AN UPRIGHT T-WAVE IN LEAD IV IN A PATIENT WITHOUT OTHER EVIDENCE OF HEART DISEASE

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NEW ORLEANS, LA.

**I**N CHILDREN an upright  $T_4$  is often seen without heart disease and alone bears no significance in diagnosis. In the adult, however, it has been described as a most significant finding. Statements that observers of wide experience<sup>1</sup> have never observed this change in the absence of "significant heart disease" justify the report of the following case.

#### CASE REPORT

H. O., aged twenty-six years, a white nurse, presented herself for a routine periodic health examination. There were no complaints and the patient considered herself in the best of health.

*Past history* revealed the following pertinent points: measles at eight years; whooping cough at ten years; and diphtheria at twelve years. The appendix was removed at the age of eighteen years. There was no history of rheumatic fever, Bright's disease, or sore throats. The venereal history was negative. Cardiorespiratory symptoms have never been noted except for a sensation of pressure in the chest, pain in the left axilla and a subjective feeling of being unable to catch her breath on one occasion a year ago. This sensation passed off in one hour and has never returned. *Personal habits* are not remarkable. She smokes rarely, but takes four to six caffeine drinks daily. *Family history* disclosed no hereditary diseases. The mother and father are living and well. *Physical examination* revealed a young white female with erect posture and sthenic habitus—height 65 inches; weight 129 pounds. Blood pressure was 128/78 in both arms; pulse, 82 per minute while sitting; after exercise (jumping 20 times on one foot) 110 per minute; after two minutes' rest 80 per minute. The thyroid isthmus was palpable. The lungs were clear.

*Heart*.—No pulsations were visible. The apex beat was palpated in the fifth left interspace just inside the midclavicular line. No abnormal pulsations were palpated. Percussion confirmed palpation. Basal dullness coincided with the manubrium sterni.  $P_2$  was greater than  $A_2$ . The sounds were otherwise not noteworthy. A soft blowing systolic murmur was heard in the pulmonic area down to the third left interspace and disappeared in the left lateral position. An occasional premature beat was heard. The *abdomen* was negative. Pelvic and neurological examinations disclosed no abnormalities. Extremities were negative.

*Laboratory Data*.—*Urine*: specific gravity, 1.020; clear; negative for albumin, casts and red blood cells; occasional pus and epithelial cells. *Stools* were negative for ova and parasites. *Blood* showed red blood cells, 4.87 million; hemoglobin, 85

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per cent; white blood cells, 9,000; differential, normal. The Wassermann reaction was negative. The basal metabolic rate was -6 per cent. *Electrocardiogram* (Fig. 1) showed normal sinus rhythm,  $T_2$  isoelectric;  $T_3$  negative;  $T_4$  upright. *X-ray film of the chest* showed that lung fields were clear. Heart measurements were: transverse, chest, 26.3 cm.; transverse, heart, 12.5 cm.; longitudinal, heart, 13.9 cm.; transverse, great vessels, 5.4 cm. *Fluoroscopy*, including that in the oblique position, with barium paste, disclosed no deviation of the esophagus and no abnormal configuration of the heart.

## COMMENT

Clinically, a diagnosis of heart disease, or possible heart disease, was impossible in this patient. All physical findings, the reaction to exer-

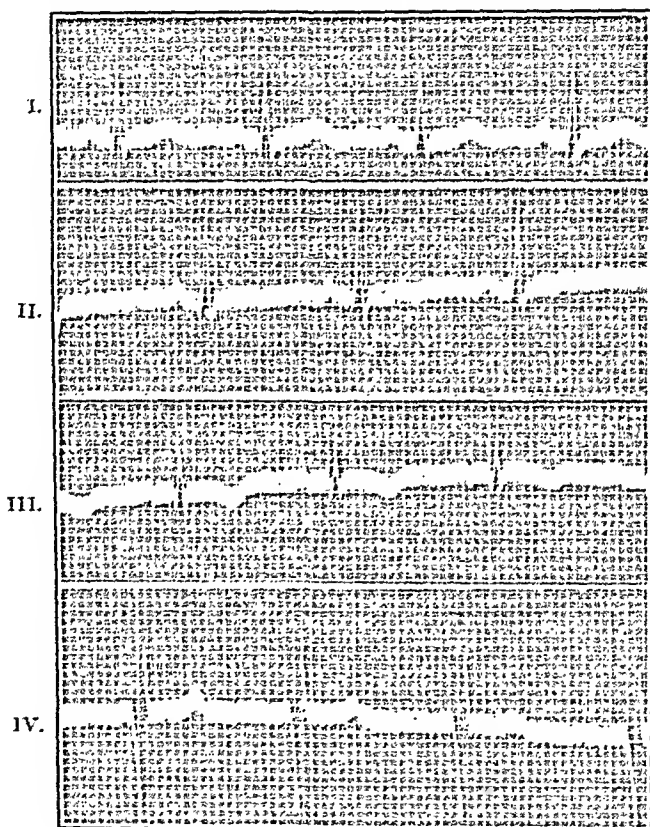


Fig. 1.

cise, as well as the reaction to usual daily activity, indicated no impairment of function. The usual pathognomonic signs of organic heart disease, such as cardiac enlargement, serious mechanical disturbances (auricular fibrillation, auricular flutter, pulsus alternans), thrills, friction rubs, diastolic murmurs, liver enlargement and other evidences of elevated venous pressure, were absent. No etiological factors such as hypertension, arteriosclerosis, hyperthyroidism, syphilis, or rheumatic fever were demonstrable. There was no precordial pain of any type. Acute rheumatic carditis and bacterial endocarditis, diseases which may be present at this age without pathognomonic signs of heart disease, were obviously not detected. In fact, significant cardiac changes or even sug-

gestive changes were absent. Extracardiac disease known to affect the heart and electrocardiogram transiently, for example, hemorrhage, was not present. The patient, to all appearances and tests, is a perfectly normal young woman.

In the past two years the electrocardiogram has been taken three times. The chest leads have been placed accurately by the author in the two repetitions according to the technique of Wolferth.<sup>1</sup> There is no technical fault. The isoelectric  $T_2$  is usually considered a suggestive sign of heart disease, but this finding again has been reported in normal individuals and cannot be considered significant.

Edeiken, Wolferth, and Wood<sup>1</sup> state, "We have not as yet seen an upright  $T_4$  in an adult in whom we were at all confident that 'there was no significant heart disease' unless the patient had received digitalis." They criticize the statement of Levine and Levine<sup>2</sup> who reported upright  $T_4$  in two patients without "significant heart disease" but with uremia and hemorrhage, respectively, both of which are known to produce T-wave changes. In the present patient no known cause except the possibility of an old diphtheritic myocardial lesion could be found to explain the  $T_4$ . Three examinations in two years have all disclosed the upright  $T_4$ . That evidence of heart disease may appear in the future is possible, but in two years' observation no such findings have developed.

#### SUMMARY

A patient without demonstrable heart disease or extracardiac disease producing T-wave changes has been known to have an upright  $T_4$  for two years. While this finding, as the single definite electrocardiographic abnormality, should be considered highly important, it appears to occur at times in the absence of "significant heart disease."

#### REFERENCES

1. Edeiken, J., Wolferth, C. G., and Wood, F. C.: AM. HEART J. 12: 666, 1936.
2. Levine, H. D., and Levine, S. A.: Am. J. M. Sc. 191: 98, 1936.

## Department of Reviews and Abstracts

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### Selected Abstracts

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Heckmann, K.: Graphic Recording of the Variations in Intensity of the Heart Shadow in Mitral Insufficiency Recorded With a Photoelectric Cell (Actinocardiogram). *Klin. Wehnschr.* 15: 928, 1936.

The author has developed a method of recording the intensity of the shadow cast by the heart under roentgenogram on the viewing screen by means of a photoelectric cell, three-stage radio amplifier and oscillograph. This is used as an index of volume changes of the heart. In mitral insufficiency he found that the cardiac pulsations decreased, and the curve shows a systolic increase in volume (the inverse of normal) followed by a decrease. During diastole, a slight volume increase (or no change) was noted followed by a marked auricular decrease. These changes are caused by the systolic regurgitation of blood from the left ventricle into the left auricle and pulmonary vessels.

L. N. K.

Diebold, O., and Mertens, O.: Central Nervous Regulation of Cardiac Minute Output During Inhalation of CO<sub>2</sub>, Rich Air. *Pflügers Arch. f. d. ges. Physiol.* 237: 585, 1936.

The blood flow in the main or left branch of the pulmonary artery was measured with a Rein thermostromuhr and from this cardiac minute volume was determined. CO<sub>2</sub> in concentrations of 5 to 12 per cent in the inspired air decreased the minute output of the heart. This decrease was obtained only when the vagi were intact.

L. N. K.

Wöhlisch, E., and Clamann, H. G.: The Elastic Properties of the Resting Heart. *Pflügers Arch. f. d. ges. Physiol.* 237: 590, 1936.

The author determined the curve of tension/length ratios of isolated heart muscle strips and also the curve of pressure/volume ratios of resting hearts. The ratios never gave a straight line relationship. In comparison to other muscles investigated the heart muscle had the least resistance to stretch.

L. N. K.

Goldenberg, M., and Rothberger, C. J.: Action of Veratrin on Purkinje Fibers. *Pflügers Arch. f. d. ges. Physiol.* 238: 137, 1936.

Small doses of veratrin cause acceleration and increase in the size of the beat of isolated Purkinje fibers obtained from the dog's heart, and at the same time the electrogram, but not the mechanogram, is prolonged. Larger doses are the cause of paroxysms of tachycardia with pauses between. Long after-potentials are demonstrated to occur in the electrogram (similar to that in nerve and ordinary muscle).

L. N. K.

Weicker, B.: Adrenalin and Metabolism of the Warm-Blooded Heart. Arch. f. exper. Path. u. Pharmacol. 181: 525, 1936.

In the cat's Langendorff heart with practically normal lactic acid content, adrenalin in therapeutic doses caused no change in the phosphoric acid fraction. With toxic doses an increase was found in the phosphoric acid and hexosephosphate content (due to the breakdown of phosphagen and adenylypyrophosphate).

In the hypodynamic Langendorff heart adrenalin in therapeutic doses caused a disappearance of phosphoric acid (and a restitution of its precursors). This occurs only in the presence of oxygen and fails to occur when the heart is kept under anaerobic conditions. Strophanthin has actions similar to adrenalin.

L. N. K.

Lissak, K., and Hoyos, G.: Loss of Albumin of Working Heart Muscle. Arch. f. exper. Path. u. Pharmacol. 181: 607, 1936.

Albumin can be demonstrated by precipitation and anaphylactic reactions in the Ringer perfusate obtained from a frog heart perfused by the method of Straub. Stimulation of vago-sympathetic fibers causes an increase in the albumin in the perfusate.

L. N. K.

Döring, G.: Experimental Production of Left Ventricular Hypertrophy by Injections of Ephedrine-Ephetonin. Beitr. z. path. Anat. u. z. allg. Path. 96: 309, 1936.

In rabbits, subcutaneous injections of ephedrine or ephetonin (0.05 mg. per day) for several months cause chronic hypertension. This led, after 69 to 107 days, to left ventricular hypertrophy in 5 animals; this is accompanied by a right ventricular hypertrophy due to stasis in the pulmonary circuit. In acute hypertension left-sided dilatation could be shown. In 4 animals kept on this regime for 135 to 164 days, no hypertrophy could be demonstrated. This was due to the disappearance of the hypertension after the one-hundredth day. This suggests that hypertrophy is a reversible process. (This idea requires further confirmation.)

L. N. K.

Henze, C.: The Pressor Receptor Fibers in the Vagus. Arch. internat. de pharmacodyn. et de therap. 53: 44, 1936.

Following section of the vagi, a rise in blood pressure can occur in an animal in which the carotid sinuses and aortic roots have been denervated previously. This is interpreted as indicating pressor fibers coming from the heart itself. The pulmonary pressure did not change under these circumstances.

L. N. K.

Sylla, A.: Slowing of the Heart With Deep Inspiration. Klin. Wochenschr. 15: 849, 1936.

In 1,000 students slowing of the heart was found in inspiration and in inspiratory arrest. It occurred in abdominal breathing but often failed to appear with exaggerated costal breathing when the diaphragm did not move much. In certain tachycardias a similar slowing was found when the diaphragm was deeply depressed during inspiration.

L. N. K.

Alam, M., and Smirk, F. H.: Observations in Man Upon a Blood Pressure Raising Reflex Arising From the Voluntary Muscles. *J. Physiol.* 89: 372, 1937.

A blood pressure raising reflex can be demonstrated in normal subjects by a simple clinical method in which a standard exercise test is used. In these experiments one extremity, usually an arm, is used in performing the test. Increases in systolic blood pressure from 5 to 85 mm. of mercury occur during the exercise test. The increase in the diastolic pressure is usually less than the increase in the systolic pressure. Various experiments indicate that the rise in blood pressure is caused by substances liberated during the muscular work and is not dependent upon the method of arresting the circulation, nor does it occur as the result of pain or mental effort. It seems that this reflex is designed so that the voluntary muscles as they become fatigued may call upon the central nervous system to regulate the supply of blood in their favor.

E. A. H.

Cossio, P., Del Castillo, E. B., and Berconsky, I.: Investigation of Blood Velocity After Exercise. *Rev. argent. de cardiol.* 3: 409, 1937.

Both the circulation time of the blood (intravenous injection of 20 per cent "deeholine") and the heart rate, before and after exercise (30 flexion movements of the legs in one minute), were investigated in 82 persons lying in a recumbent position: 10 entirely healthy people, 7 suffering from severe impairments other than cardiac disease (cancer of the stomach, leucemia, etc.), 6 with hyperthyroidism, and 59 with structural alterations of the heart. The magnitude of the reduction in the circulation time after exercise has been considered to be an index of the so-called reserve power of the heart, under the assumption that the heart output is the fundamental factor governing the speed of the blood flow.

In the group of 10 healthy people, the decrease in the circulation time varied from 0 to 17 per cent in three sedentary persons, and from 29.9 to 46.1 per cent (average 31.8 p. c.) in active individuals, some of them devoting much of their time to athletic activities. There was no relation between the decrease of circulation time and the increase in heart rate.

In the group of severely ill people without cardiac involvement, the reduction in the circulation time after exercise varied from 5 to 15 per cent (except in one case in which the reduction reached 23 p. c.). The heart rate increased from 20 to 75 per cent but with no relation to the decreased circulation time.

In the hyperthyroidism group, while 4 patients showed a decreased circulation time, the reduction varying from 0.6 to 26 per cent, in two cases a prolongation of the time was found, a type of reaction which we qualified as paradoxical.

Among the group of cardiac patients, in 7 the decrease in circulation time amounted to at least 27 per cent; in another 30 it was less than 25 per cent; in 7 there was no appreciable change, and in the remaining 15 patients a paradoxical reaction was observed. To explain the latter, an increased initial tension of the cardiac fiber beyond the critical value has been assumed.

AUTHOR.

Korth, C., and Schrumph, W.: Reciprocal Rhythm. *Deutsches Arch. f. klin. Med.* 178: 589, 1936.

A case of sinoauricular block is described in which the electrocardiogram showed coupled beats which are attributed by the author to reciprocal rhythm. In each pair of beats, the first is from the A-V node. It is conducted back to the auricle later than to the ventricle, and this auricular impulse then returns to restimulate the

ventricles. The conditions for reciprocal beating are fulfilled in the case described, viz.: (a) undisturbed action of an automatic A-V rhythm at a slow rate at the lower end of the node and (b) retrograde conduction.

L. N. K.

Hecht, H.: Precordial Leads in Clinical Electrocardiograms. *Deutsches Arch. f. klin. Med.* 179: 1, 1936.

The author used two precordial regions for the exploring electrode (third interspace to the right of the sternum and the sixth interspace over the apex), his fixed electrode being the null point electrode of Wilson. The contour of the records in 200 normal and cardiac patients is described. In left preponderance a flattening of T was found in the apical lead; in right preponderance a reversal of all the complexes was found in the basal lead. This permitted him to distinguish between axis shift and preponderance. The value of these leads in flutter and fibrillation of the auricles is emphasized, and they show changes in S-T and T-waves early in abnormal hearts.

L. N. K.

Spühler, O.: Adams-Stokes Syndrome. *Ztschr. f. klin. Med.* 129: 693, 1936.

The author finds that Adams-Stokes syndrome is caused as often by transient ventricular fibrillation as by standstill of the heart.

L. N. K.

Marzahn, H.: Electrocardiographic Studies During Work. *Ztschr. f. klin. Med.* 130: 135, 1936.

When work caused an acceleration of the heart to 200 beats per minute, the author found that the QRS span was shortened by 0.01 second. Extrasystoles tended to appear, but extrasystoles present at rest tended to disappear. No difference was noted in the appearance, disappearance, and magnitude of the cardiac acceleration between normal and cardiac patients. An acceleration was found following exercise in patients with complete heart-block.

L. N. K.

Comeau, Wilfrid J.: Paroxysmal Complete Heart Block Alternating With Normal Rhythm and Conduction. *Am. J. M. Sc.* 194: 43, 1937.

The literature of recurrent complete heart-block alternating with normal conduction and accompanied by Adams-Stokes syndrome has been examined critically. Of 20 potential cases discovered in the literature, 12 have been accepted as complying with the criteria established. The important clinical, pathological, and electrocardiographic data of these cases have been summarized.

A case, a woman aged seventy-eight, with Adams-Stokes syndrome, is presented in which, as shown by electrocardiographic evidence, complete heart-block alternated with normal rhythm and conduction. The results with atropine demonstrated that the changes probably occurred independent of any vagus effect. This case ultimately developed a chronic complete block with the spontaneous disappearance of the syncopal attacks.

The form of the transition from one degree of conduction to another, as shown by graphic tracings, is summarized.

The practical diagnostic and therapeutic considerations of this condition are emphasized.

The pathogenesis of paroxysmal complete heart-block is discussed. It is probable that the majority of cases are on an arteriosclerotic basis and that either a fibrocalcereous mass or fibrosis due to coronary sclerosis partially damages the bundle of His. The fluctuating character of the conduction in these cases is probably determined by temporary variations in the local circulation to the remaining intact fibers.

AUTHOR.

Grosse-Brockhoff, F., and Strotmann, A.: The Time Relation Between Mechanical Systole and the Electrocardiogram. *Ztschr. f. d. ges. exper. Med.* 98: 227, 1936.

The volume curves and optical carotid artery pressure curves were recorded in anesthetized rabbits, simultaneously with Lead I of the electrocardiogram. No constant relation was found between the end of the T-wave and the end of the mechanical systole. It was found that the Q-T interval is not equal to the duration of the mechanical systole, and the ratio between the two is inconstant. One cannot judge the duration, let alone the power of systole from the electrocardiogram.

L. N. K.

Heim, F.: Conduction Disturbances in Human Heart. *Ztschr. f. d. ges. exper. Med.* 98: 551, 1936.

The relation of the P-R interval to the duration of the cycle is determined and shown to give a smooth curve. It is shown that the P-R interval does not lengthen as much as anticipated following interpolated auricular extrasystoles, presumably because the refractory period is shortened as the heart rate accelerates. The Wenckebach phenomenon in the digitalized heart with A-V block is attributed to progressive lengthening of the refractory period from beat to beat until a ventricular beat is dropped and the refractory phase is shortened again.

L. N. K.

Zárday, I. V.: Electrocardiographic Studies of the Auricles. *Ztschr. f. d. ges. exper. Med.* 98: 662, 1936.

The author used unipolar chest leads and could distinguish the action of each of the auricles. He demonstrated an asynchrony of 0.01 to 0.09 second between the onset of electrical activity in the two auricles. Leads I and III, according to the author, give only the P-wave of the left auricle, while the P-wave in Lead II is a summation of the activity of the two auricles. Splintering of  $P_2$  is due to interauricular block, and this block is the cause for a difference in the P-R interval in Leads I and II. (The interesting observations need confirmation.)

L. N. K.

Lewis, Thomas: Auricular Flutter Continuing for Twenty-Four Years. *Brit. M. J.* 1: 1248, 1937.

The case is of exceptional interest for three reasons. First, the auricles seem to have fluttered without cessation for twenty-four (if not twenty-seven) years. Secondly, although the ventricle during the greater part of the period has been driven at very excessive rates, the efficiency of the heart has not been impaired by its increased energy expenditure. Thirdly, the rate of auricular beating has fallen about 80 beats per minute. This fall might be attributed to lengthening of the circular path around which the wave travels, or more probably to its slower speed of movement. It would be interesting to know if lowering of rate is usual in auricular flutter as age greatly advances.

AUTHOR.

Arieff, M. J., Wituschinsky, W. J., and Rabinerson, A. B.: The Collateral Circulation of the Heart in Syphilitic Meso-aortic Closure of the Mouths of the Coronary Arteries and in Adhesive Mediastinopericarditis. *Ztschr. f. klin. Med.* 130: 153, 1936.

Collateral vessels in the heart come either from enlargement of vessels already present or from the development of new vessels. In syphilitic closure of the coronary vessel mouths, the collaterals between the right and left coronary arteries form the new vessels. In mediastinopericarditis, the new vessels come from anastomoses with extracardiac vessels, chiefly those of the lung and diaphragm.

L. N. K.

Hafkesbring, Eleanor M., Drawe, Catherine E., and Ashman, Richard: I. Measurements for One Hundred Normal Children. *Am. J. Dis. Child.* 53: 1457, 1937.

To establish trustworthy criteria for the normal electrocardiogram of the child, electrocardiograms of 100 normal children were selected and the heights of the individual deflections in each lead as well as the time relations of the various intervals and phases of the cardiac cycle were carefully measured.

The duration of the P-wave was found to average 0.062 second. The upper limit we would consider to be 0.09 second or perhaps 0.085 second, since a P-wave measuring 0.09 was found in only 1 case.

Since the height of the P-wave in Lead I was slightly higher than the average for the normal adult, the upper limit should be placed at about 1.5 mm. or a little lower. A P<sub>2</sub> measuring over 2.5 mm. should be considered above the normal.

A diphasic or slightly inverted P<sub>2</sub> is occasionally found in the electrocardiogram of a normal child.

Slight and questionable notching of the P-wave is occasionally seen, but no definite or conspicuous notching of the P-wave is found in the electrocardiogram of a normal child.

The average P-R for our series was 0.132 second, and there was no significant difference according to sex. We found that the P-R interval tended to increase with increasing age and to decrease with increasing heart rate. We believe that instead of setting one definite figure for the upper limit of normal for children's electrocardiograms it would be a better plan, if sufficient data were available, to secure a statistically significant average for each age and heart rate and to construct a table giving the upper limits of the P-R at the various ages and heart rates. If a more reliable approximation of the size of the heart were available (perhaps the surface area, as suggested by Kissane), this could be used in the table instead of the age.

The average duration of the QRS group was 0.065 second. The QRS showed an increase in duration with the increase in age. We agree with other authors in placing the upper limit for duration of the QRS for children at 0.09 second, or at less for young children and infants. QRS of low voltage was found in only 1 of 100 electrocardiograms of normal children. There is no great difference between the heights of the R-wave for children and those for the R-wave of adults. We found the average to be slightly higher for children. Other authors have found it much higher and others lower.

Slight slurring of the deflections of the QRS may be found, frequently of the R-wave in Lead II, but definite or conspicuous slurring is almost never found in an electrocardiogram of a normal child.

The electrical axis in all but 3 cases lay between 20 and 104 degrees, ranging from a slight left axis deviation to a slight right axis deviation.

Slight shifting of the RS-T segment, especially upward, is occasionally seen in a normal child's electrocardiogram.



The T-waves consistently averaged higher for the boys than for the girls, even when the data were separated according to the various age groups. We have no explanation of this difference. It will be seen in Part II that this difference according to sex is also found in the electrocardiograms of children with heart disease.

T<sub>2</sub> frequently inverted or diphasic in the electrocardiogram of the normal child.

Low T-waves were found in only 1 case, and the normality of this picture should be doubted, since T<sub>2</sub> was slightly diphasic. No notched T-waves were found.

Like many previous investigators, we found the Q-T to vary with the heart rate, but we found no difference according to sex, such as is found in the electrocardiograms of adults.

Premature beats are rare in children with normal hearts.

AUTHOR.

Drawe, Catherine E., Hafkesbring, Eleanor M., and Ashman, Richard: II. The Changes in Children's Electrocardiograms Produced by Rheumatic and Congenital Heart Disease. *Am. J. Dis. Child.* 53: 1470, 1937.

The electrocardiograms of 100 children with rheumatic heart disease and of 50 children with congenital heart defect were carefully measured (the heights of the individual deflections and the various intervals of the cardiac cycle), and the averages for the different intervals were compared with those found in the electrocardiograms of the normal group (Part I).

The Rheumatic Group.—The principal abnormalities of the P-wave in the electrocardiograms of children with rheumatic heart disease are definite and conspicuous notching, widening, and slight increase in height.

The P-R interval is definitely prolonged in a large percentage of cases of rheumatic heart disease.

The abnormalities of the QRS complex are relatively slight, consisting of a small increase in duration and occasional notching or slurring of the individual waves.

Only a slight tendency to right axis deviation was shown in the electrocardiograms of children with mitral stenosis and insufficiency. This was probably due to the fact that in most of our cases the condition was not far advanced. The children with aortic regurgitation showed a definite tendency to left axis deviation.

The incidence of shifts of the RS-T segment is increased, but not so markedly as had been reported elsewhere. However, we were unable to follow our patients closely and to make additional electrocardiograms during the course of the rheumatic fever.

Abnormalities of the T-waves were found in 10 per cent of the cases. These abnormalities consisted of low T-waves in all leads (below 1 mm.), diphasic T-waves in Lead I, and low, rounded, notched, and inverted T-waves in Lead II.

The Q-T interval is often definitely prolonged in cases of rheumatic heart disease.

As with the normal children, the incidence of premature beats is low.

Not all children with rheumatic heart disease have abnormal electrocardiograms.

Even though the electrocardiogram of a child is not definitely abnormal the presence of any one of the aforementioned abnormalities should suggest the possibility of rheumatic heart disease.

The Group With Congenital Defect.—The outstanding abnormalities of the P-wave were an increase in the width and in the height, and these were found chiefly in the electrocardiograms of children with pulmonary stenosis and tetralogy of Fallot and to a lesser degree in those of children with interventricular septal defect. The notching of the P-wave was not beyond normal limits.

The P-R interval was approximately the same as it was in the electrocardiograms of the normal group, but it may be considered to have been slightly prolonged

on the average, since the children's mean age was a few years younger in the group with congenital heart defect than in the normal group.

The average duration of the QRS in the electrocardiograms of children with congenital heart defect was longer than that in the electrocardiograms of normal children, even though the children were younger. This increase in duration was due mainly to the influence of the children with pulmonary stenosis.

Notching and slurring of the QRS occurred frequently in the electrocardiograms of children with pulmonary stenosis, occasionally in those of children with interventricular septal defect and rarely in those of children with patent ductus arteriosus.

All the electrocardiograms of children with pulmonary stenosis showed extreme, conspicuous or definite right axis deviation, ranging from 99 to 179 degrees, and in 1 case, not included when the average was computed, the deviation was 125 degrees.

The T-waves averaged considerably higher than those in the electrocardiograms of the normal group. As with the normal children, the boys' T-waves averaged higher than those of the girls.

Abnormalities of the T-waves are occasionally found, consisting of inversions of  $T_2$  and deep inversions of  $T_3$ .

The Q-T interval was slightly prolonged in a few instances.

AUTHOR.

Gross, Louis, and Silverman, Gertrude: The Aortic Commissural Lesion in Rheumatic Fever. *Am. J. Path.* 13: 389, 1937.

There has been described in this report the findings in 70 cases of rheumatic fever segregated into six groups according to the clinical course taken by the disease. It is shown that a number of inflammatory changes are found in the aortic root, wedge, annulus, ring, subaortic angle, and pericardial mantle which are characteristic of rheumatic fever and, to some extent, reflect the clinical course of the disease. Even when healing takes place the histological characteristics of the commissural lesion afford additional stigmata which are of value in discerning a past rheumatic process. A discussion is given of the pathogenesis of this lesion from which it appears that even though the original infection may reach the aortic ring through several routes, in most instances the inflammatory granulation tissue passes from the pericardial mantle through the aortic root, wedge, and annulus to reach the aortic rings. The latter show a much more flagrant inflammatory process which spreads into the valve leaflets and, probably with the additional factor of trauma caused by the systolic and diastolic movements of the cusps, eventually leads to their agglutination. The possible significance of these findings in relation to the pathogenesis of the so-called congenital bicuspid aortic valve is indicated. A description is also given of the histological and topographical changes taking place during the different age periods in the normal aortic commissural region.

AUTHOR.

Hess, L.: Pathology of Syphilitic Aortitis. *Klin. Wehnschr.* 15: 898, 1936.

In this presentation the author shows that 62 per cent of the cases of syphilitic aortitis had a heredity of vascular disability, which is much higher than in a control series. He considers this of significance in the occurrence of vascular involvement in syphilis.

L. N. K.

Porter, R. E., and Gordon, Wm. H.: The Size of the Heart in Pulmonary Tuberculosis. *Am. Rev. Tuberc.* 36: 82, 1937.

A study was made of the teleoroentgenograms of 400 patients having pulmonary tuberculosis.

Their ages ranged from eighteen to sixty-seven years.

The study included all clinical types of pulmonary tuberculosis.

A comparison was made between the measured transverse diameter of the heart and the predicted transverse diameter.

Of the 400 patients, 203 (50.5 per cent) had a measured transverse diameter greater than the predicted diameter, 165 (41.5 per cent) had a measured transverse diameter of less than the predicted diameter and 32 (8 per cent) had a measured transverse diameter equal to the predicted diameter.

As is shown in Table 2, in a study of the x-ray films of the 54 patients that died, there was very little difference noticed as compared with the general average.

AUTHOR.

Leubner, H.: Rare Cancers of Blood Vessel Endothelium. Frankfurt. Ztschr. f. Path. 49: 63, 1936.

A case of hemangioendotheliomatosis of the liver, spleen, and skin in a twenty-six-year-old man is described which is interpreted as a primary multiple cancerous growth. A second case of diffuse lymphangioendothelioma in an eighteen-year-old boy is reported. This caused elephantiasis of the genitalia, abdominal wall, and both extremities. This was also found to be cancerous on histological examination.

L. N. K.

Radaseh, H. E.: Glomal Tumors. Arch. Path. 23: 615, 1937.

Ninety glomal tumors have been reported to date. They have a wide anatomical distribution. Once elassed as angiomas, they are now known to result from hyperplasia of an arteriovenous anastomosis (digital glomus). The normal glomus is a distinct structural unit or organ consisting of an afferent arteriole, a Suequet-Hoyer canal, a primary collecting vein, intraglomerular reticulum, and a capsular portion.

The article deals largely with anatomical and pathological structure, but quotes articles in which physiological deductions are made. For instance, the normal glomus may play an important part in the regulations of peripheral blood flow, of blood pressure, and of temperature regulation by heat loss.

Glomal tumor is typically attended by exquisite tenderness over the tumor and by considerable pain over a wide area surrounding the tumor. Excision is the only treatment, and is universally effective.

H. M.

Beneke, R.: Intimal Fibrosis (Endarteriitis obliterans) as a Sequel to Local Flow Anomalies. Ztschr. f. Kreislaufforsch. 29: 146, 1937.

The argument is presented that intimal fibrosis results from abnormalities in flow at the site of fibrosis.

L. N. K.

Baker, A. B.: Structure of the Small Cerebral Arteries and Their Changes With Age. Am. J. Path. 13: 453, 1937.

This investigation was made because there are few reports on the structure of normal cerebral vessels. Quoting from the "Conclusions": The average small cerebral artery differs in structure from similar sized vessels elsewhere in the body in that it contains within its media a relative paucity of both elastic and

muscle tissue and a predominance of collagenous fibers. The very small cerebral arteries are composed almost strictly of collagenous tissue and may appear as a cerebral fibrosis. With the advance of age the elastica interna of the cerebral arteries becomes reduplicated and frequently loses its normal tinctorial properties. The media undergoes a rapid fibrosis. It frequently shows a hyalinization and more rarely a calcification of all of its elements.

H. M.

Schretzenmayr, A.: The Rôle of the Medium and Large Arteries in Regulating the Circulation. *Klin. Wehnschr.* 15: 625, 670, 1936.

The author's studies with arterial oncometry show that the medium and large vessels play an important rôle in regulating the circulation. (This is not convincing.) These studies also show that sclerosis of the large vessels noticeably alters the work of the heart.

L. N. K.

Gebert, W.: Capillary Function and Menstruation. *Klin. Wehnschr.* 15: 828, 1936.

The latent period in developing dermographia was determined at various times in the menstrual cycle. Preceding menstruation, the latent period at first decreases and then increases until menstruation begins, after which it decreases rapidly to normal.

L. N. K.

Roboz, P.: Capillary Function Tests. *Klin. Wehnschr.* 15: 968, 1936.

The velocity of skin capillary flow is determined under the microscope (1) at room temperature and (2) after immersion in water at a temperature of 50° C. for ten minutes. The usual effect of heat is to make the flow so rapid that the movement of the red blood cells cannot be measured. In certain instances, however, the heat causes stasis.

L. N. K.

De Takats, Geza, Hick, Ford K., and Coulter, John S.: Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease. *J. A. M. A.* 108: 1951, 1937.

The authors present a method of comparing the peripheral vascular effects of intermittent venous hyperemia and of intermittent suction and pressure by means of oscillometer curves and venous oxygen determinations. They state that "the paucity of data does not permit conclusions;" also that "certain variable factors make comparable controls very difficult."

H. M.

Schneyer, K.: Observations on the Peripheral Circulation by Experimental Aortic Insufficiency. *Arch. f. exper. Path. u. Pharmacol.* 181: 481, 1936.

Microscopic examination of the rabbit's mesentery showed a vasoconstriction following production of aortic insufficiency by valve destruction. This vasoconstriction does not occur when the four blood pressure regulator nerves (the carotid sinus and aortic nerves) are sectioned. No capillary pulse was observed in the rabbit following production of aortic insufficiency but exaggeration of the pulsatory movement in the larger arteries was noted in the microscopic field.

L. N. K.

Wezler, K., and Standl, R.: The Normal Age Curve of Pulse Wave Velocity in Elastic and Muscular Arteries of Man. *Ztschr. f. Biol.* 97: 265, 1936.

The curves of the pulse wave velocities for the aorta and of the arteries of the arm and leg at various ages are given. These are related to the changes in elasticity of these vessels. The earlier age at which acceleration of the pulse wave velocity occurs in the leg as compared to that in the arm indicates earlier sclerosis of the vessels in the leg.

L. N. K.

Gross, D.: The Clinicostatic Respiratory Signs in Decompensated Cardiac Patients. *Ztschr. f. Kreislaufforsch.* 29: 113, 1937.

The influence of the recumbent position on vital capacity and breath holding was determined in twenty individuals without heart disease and twenty with cardiac disease and various degrees of congestive heart failure. These values were determined in the reclining and sitting positions. In well persons little or no change on vital capacity or breath holding was found. In cardiac patients a noticeable reduction of vital capacity and breath holding was found. This is used as a clinicostatic index of heart function. (An examination of tables shows that the effect of posture, by and large, is proportional to the reduction below normal of the vital capacity and breath holding.)

L. N. K.

Lucas, M.: Air Emboli in Coronary Arteries Following Artificial Pneumothorax in a Thirty-Year-Old Patient. *Beitr. z. Klin. d. Tuberk.* 88: 223, 1936.

In refilling an old left-sided pneumothorax a pulmonary vein was entered and a fatal air embolism resulted. In addition to air emboli in the cerebral vessels a massive air embolus of the left coronary artery was demonstrated postmortem. There were hemorrhagic areas of necrosis in the wall of the left ventricle. Death in this case was preceded by tachycardia and unconsciousness.

L. N. K.

Radnai, P., and Mosonyi, L.: Venous Air Emboli. *Ztschr. f. d. ges. exper. Med.* 98: 755, 1936.

In acute air embolism of venous origin air can be demonstrated in the left side of the animal's heart both by roentgen ray and postmortem. The results of air injection as far as death is concerned are not predictable. Electrocardiographic changes are found indicating disturbances in coronary circulation. These are reversible in animals that survive.

L. N. K.

Blalock, Alfred, Robinson, C. S., Cunningham, B. S., and Gray, Mary E.: Experimental Studies on Lymphatic Blockage. *Arch. Surg.* 34: 1049, 1937.

Complete blockage of the lymphatic system has never been produced experimentally. The explanation of this fact must lie in the capacity for the development of a collateral circulation. Experiments have been performed on 52 dogs and 22 cats in which an attempt was made to produce a complete blockage of the lymphatics by various procedures which included ligation and the injection of sclerosing agents into the lymphatics. In three of the animals, complete lymphatic blockage was produced. This resulted in an almost complete disappearance of the lymphocytes and eosinophiles from the blood stream. The animals lost weight and were killed when it became apparent that they were going to die. Examination at autopsy revealed

the lymphatics of the abdominal organs to be markedly distended and there was extravasation of chyle into many of the tissues. No lymphaticovenous communications could be determined. In the other animals, the lymphatic obstruction was temporary. In these animals, a similar but temporary change was noted in the blood picture.

E. A. H.

Lazarovits, L.: Aortic Pain and X-ray Irradiation. *Wien. klin. Wchnschr.* 49: 755, 1936.

The author used x-ray irradiation in 27 cases of pain due to syphilitic aortitis. He used 50 per cent of the erythema dose and radiated both from the front and back; as many as 10 treatments were used. In 11 of these patients a lasting and definite relief of pain was found. Patients having angina pectoris were not relieved.

L. N. K.

Gold, Harry, Kwit, Nathaniel T., and Otto, Harold: The Xanthines (Theobromine and Aminophylline) in the Treatment of Cardiac Pain. *J. A. M. A.* 108: 2173, 1937.

The effect of theobromine and aminophylline on cardiac pain was studied in a group of 100 ambulant patients with angina pectoris.

These patients were selected on the basis of proof of organic heart disease, cardiac pain on effort, little or no physical work, and faithful cooperation.

An attempt to include only patients who could distinguish relief afforded by glyceryl trinitrate from relief by a soluble placebo tablet taken in the same way during an attack of pain was abandoned, because a fairly large number of patients with cardiac pain were found who could not distinguish between the two. This is due to the transient character of effort pain in a large proportion of the patients.

The effect studied was the influence on the severity and frequency of attacks and on the capacity for effort without pain, not relief during attacks of pain.

The data consisted of the patients' judgments regarding changes in pain. These data were secured in a manner relatively free of bias by the use of the "blind test."

In all, 209 courses of treatment with the xanthines were given, each course being alternated with a course in which a placebo (or some other agent) was used.

The doses of the xanthines were from 15 to 60 grains daily of theobromine, and from 9 to 12 grains daily of aminophylline.

Changes in the amount of pain were charted. Cause and effect were established by a method relatively free of personal judgments; namely, by comparing sections of the chart representing periods in which a placebo of lactose (or some other agent) was taken with those in which a xanthine was administered.

The xanthines were without appreciable influence on the blood pressure.

Every type of change in pain observed during the use of a xanthine was reproduced in the same individual by a period in which a placebo was used.

The results show, therefore, that patients with cardiac pain are unable to distinguish the effects of a placebo from those of a xanthine when measures are taken to preclude the identification of the agent by any means other than the relief of pain. It is concluded that the xanthines exert no specific action which is useful in the routine treatment of cardiac pain.

AUTHOR.

Bernhardt, H.: Effect of Cortical Hormone and Vitamin C on Circulatory Collapse of Diphtheritic Origin. *Deutsche med. Wchnschr.* 62: 1123, 1936.

The author has used, in malignant diphtheria, intravenous injections of 10 c.c. of an adrenal cortical hormone, 2 c.c. of Vitamin C preparation, 20 c.c. of 10 per cent

glucose and 5 to 10 c.c. of NaCl. He found the results very satisfactory and obtained relief of the symptoms of circulatory collapse. The procedure should be used immediately when signs appear. Small repeated doses are better than a single large one. This medication works better than camphor, cardiazol, or coramin. Digitalis is counterindicated in the condition.

L. N. K.

Külbs, F.: The Clinical Significance of Heart Enlargement. *Med. Klin.* 32: 522, 1936.

Regulation of patients' activities and small doses of digitalis permit long life in patients with auricular fibrillation and large hearts. When congestive failure is present, intensive medication with digitalis and strophanthus is indicated.

L. N. K.

Kisch, F.: Therapy in and Criteria for Judging Effect in Intermittent Claudication. *Wien klin. Wchnschr.* 49: 712, 1936.

The author used an exercise test to determine efficacy of treatment. This consisted in determining the number of flexions of the limb at the knee which cause pain when the patient is lying flat in bed. Both nitroglycerine and euphyllin cause an increase in the exercise tolerance in patients with intermittent claudication; in some instances, in fact, pain could not be elicited after therapy. The author has used prolonged medication with nitroglycerine and euphyllin—the former under the tongue, and the latter intravenously or as a suppository—in ten patients with intermittent claudication. Marked improvement was observed in five of these patients in the course of a year, the improvement was slight in two others and absent in the remaining three.

L. N. K.

Weiss, Soma: Vagal Reflex Irritability and the Treatment of Paroxysmal Auricular Tachycardia With Ipecac. *Am. J. M. Sc.* 194: 53, 1937.

Ipecac is a useful agent in the treatment of paroxysmal auricular tachycardia.

In 11 cases attacks were relieved following the oral administration of doses of from 4 to 32 c.c. (1 to 8 drams) of syrup of ipecac.

The pharmacologic principle underlying this method of treatment and the considerations to be observed in its application are described.

The relation of the physiologic state of the autonomic nervous system, and particularly of the sensory-vagal reflexes, to the effective treatment of paroxysmal auricular tachycardia is discussed. The more powerful the vagal stimulus applied and the more increased the tonus of the specific reflex, the greater is the probability of therapeutic success.

The pronounced variations in the tonus and in the irritability of the various cardiac inhibitory reflexes are the basic causes underlying the variability of effectiveness of measures used in the treatment of paroxysmal auricular tachycardia.

AUTHOR.

# The American Heart Journal

VOL. 14

OCTOBER, 1937

No. 4

## Original Communications

### FACTORS AFFECTING VASCULAR TONE\*

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THE honor of giving the first of the George E. Brown Memorial Lectures I appreciate highly. Although my ways and the ways followed by Dr. Brown crossed at many points, it happens that I never had the privilege of meeting him. It would have been a privilege, indeed, for he had many experiences which were related to mine and which would have led, I am sure, to a stimulating exchange of ideas.

As a young man he had his internship in a small railroad hospital in northern Minnesota. For ten years he practiced medicine in a community of about 10,000 people in Montana. Those were conditions for knowing many kinds of human beings—trainmen, ranchers, cowboys, and the families of a newly settled country. The quality of the man is revealed better than in any verbal testimony by his being among the first in Montana to utilize the tuberculin test, the Wassermann reaction, and the fluoroscope. It is revealed also by his repeated resort to eastern centers for special studies which would render him more useful to those whom he served.

In 1921 his eagerness to contribute to the progress of medicine, besides being a helpful physician, led him to accept a position at the Mayo Clinic. There he continued in activity for nearly fifteen years. During that period his name became known widely through his own country and abroad because of his important contributions to our knowledge of blood vessels and their disorders. His bibliography includes a list of 140 papers, the great majority of which were devoted to studies of vascular disease. It is of interest that as early as 1923 he reported on a case of malignant hypertension, and in the years which followed he and other members of the Division of Medicine at the Mayo Clinic described numerous other cases and observations related to disorders of the circulatory system.

\*George E. Brown Memorial Lecture.

Delivered before The American Heart Association, June 7, 1937, in Atlantic City, N. J.



Dr. Brown impressed his associates by the variety of his interests, by his vivid and alert intelligence, his attention to new developments in medicine, his open-mindedness, and by his generous and stimulating attitude toward younger men with whom he came in contact. As someone has remarked, "Dr. Brown beautifully exemplified the glory of the medical guild—the desire to share not only with the community but with all of his fellows the best of his mind, his heart, and his personality." It is in a tribute to him that we gather here today to consider problems which were central in his thought.

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The accidental discovery of vasoconstrictor nerves by Claude Bernard in 1851, the prompt confirmation of that discovery by Brown-Sequard and Waller, and Bernard's demonstration of vasodilators in the submaxillary gland brought two new concepts into our understanding of the circulation of the blood. The first was the idea that the blood vessels are under control of the nervous system and therefore can be made to contract or relax and thus vary the resistance of the flow in their channels. The second idea was that the circulation can be adapted to the general requirements of the organism as a whole and also to local needs of particular organs, in accordance with variations of rest or activity. From the earliest observations on the rabbit's ear and on the salivary glands, seventy or eighty years ago, until the recent studies on carotid sinus reflexes and conditions producing hypertension, much of the interest in the physiology of the circulation has been concerned with the factors which affect the distribution of blood in the body.

For many decades studies on the control of blood vessels were fairly simply related to examination of the effects of severing the nervous connections at various points and noting what occurred, or in stimulating severed nerves in order to observe the consequences. The local reflexes of Lovén, the axon reflexes of Langley and the antidromic impulses elucidated by Stricker<sup>1</sup> and Bayliss<sup>2</sup> were revelations of significant new facts pertinent to vascular physiology. These researches on the effects of nervous agencies alone, however, have been complicated by later evidence for humoral or chemical factors which play a rôle in determining the contraction or relaxation of peripheral vessels.

To cover the entire field of the physiology of peripheral blood vessels would be obviously too great a task for a brief lecture. Much that one might say in these circumstances must be set aside, and only certain features of the vascular aspects of circulatory physiology can be considered. In the short time available I propose to consider some of the newer testimony regarding vascular tone. In using the term "vascular tone" I do not commit myself to any particular idea of the nature of the tonic state in smooth muscle or in capillary endothelium. I am using the term to designate a state of moderate contraction of the elements

in the vascular walls—a state which can be both increased and decreased by the operation of appropriate agencies. I am assuming, furthermore, that the discussion will relate only to changes in the blood vessels, i.e., that, unless otherwise specified, we may consider the cardiac pump as engaging in a steady performance. With these provisions declared, I propose that we consider together certain factors which affect the size of vascular channels and thereby produce hypotension, hypertension, and local adjustments of the circulation in accordance with local needs.

#### THE EFFECTS OF SYMPATHECTOMY ON VASCULAR TONE

In experiments on dogs, Goltz<sup>3</sup> was first to show that severance of the vasomotor nerves left a moderate state of contraction in the blood vessels. This gradually increased and, as judged by temperature, might later more than equal the original degree. The recovery of the contracted state was noted also by Dale and Richards<sup>4</sup> in the vessels of the cat's limb, the nerves of which had been cut; after initial loss of tone there was fairly rapid restoration. Furthermore, Grant and Bland<sup>5</sup> reported a return of the tonic contraction in the vessels of the rabbit's ear after the vasoconstrictor nerves had been cut.

These observations on vascular behavior after denervation in special regions of the body are in harmony with observations made on animals completely deprived of the sympathetic system. In 1931 Bradford Cannon<sup>6</sup> reported records of blood pressure of dogs from which the sympathetic chains had been removed in parts until there were left no connections between the blood vessels and the central nervous system. The sympathetic chains were extirpated in three stages: first, the lumbar sections with severance of the right splanchnics; second, removal of the right thoracic section; and finally, the left thoracic section with the left splanchnics. An immediate fall of arterial pressure occurred after completion of each stage. When the final portion of the sympathetic was taken, the pressure, after the primary drop, came to rest somewhat lower than the original level, i.e., at about 120 mm. Hg.

The blood pressure of the dogs studied by Bradford Cannon was measured by means of a pressure cuff and auscultation or palpation. The fairly normal pressure which he noted after extirpation of the last segment of the sympathetic system was confirmed for cats as well as for dogs by Bacq, Brouha, and Heymans.<sup>7</sup> They measured the arterial pressure by connecting the femoral artery with a mercury manometer. In totally sympathectomized animals they state that the recovery from low pressure is by way of a progressive return. Further evidence regarding the restoration of pressure in animals wholly deprived of the sympathetic system was reported by Wilson, Roome, and Grimson<sup>8</sup> last year. Again the return of a fairly normal blood pressure was noted. The evidence is clear from all these studies that, just as peripheral vascular tone is restored locally after local section of vasoconstrictor

nerves, there is a corresponding restoration of tone and a consequent persistence of a fairly normal arterial pressure after the sympathetic system has been entirely extirpated.

Thus far the return of normal pressure after sympathectomy has been explained as due solely to the recovery of a tonic state in the vascular walls. Conceivably the recovery is not complete. In that case the return might be aided by an increase of blood volume—an increase which would compensate for a greater capacity in the circulatory system. In studies on dogs Wilson, Roome, and Grimson<sup>8</sup> came to the conclusion that the quantity of circulating blood is not greater after complete sympathectomy than before. Their estimates were based, however, on the bleeding volume. It is questionable whether that method can yield satisfactory evidence. In the normal animal reflex vasoconstriction occurs as the blood pressure falls, and thus blood would be forced out of the vessels until the last heartbeat. In the sympathectomized animal reflex reduction of the vascular capacity cannot occur, and, therefore, a bleeding volume after sympathectomy *equal* to that in normal animals, might reasonably be interpreted as indicating a more than normal amount of blood in the vessels. There is some evidence that the blood volume is indeed greater after sympathectomy than before. Hamlin, in unpublished observations on sympathectomized cats, has found (in seven animals) that the average increase of the quantity of circulating blood was 25 per cent. His estimates were based on the use of Gregersen's well-tested blue-dye method. Four or five measurements were made before the operation and a similar number afterwards. The animals had all regained their former weight before the postoperative determinations were made. Curiously the determinations after removal of the sympathetic fibers showed wider variations than those made before. These are data which must be confirmed; they indicate, however, that the restored blood pressure after sympathectomy may be partially due to a larger amount of blood filling a more capacious system.

*Condition Affecting Physiological Tone After Sympathectomy.*—Since the observations of Meltzer and Auer<sup>9</sup> in 1904, it has been recognized that section of the sympathetic nerves supplied to smooth muscle renders the muscle more sensitive to adrenalin or secreted adrenine. Their observations were made on the blood vessels of the rabbit's ear and also on the cat's iris and nictitating membrane. These facts have been repeatedly confirmed by other observers and have been extended to smooth muscle in other parts of the body. About two years ago Hampel<sup>10</sup> reported on the rate of development of sensitiveness as manifest in the smooth muscle of the nictitating membrane. During the first week there is a rapid gain, which is followed by a slower gain during the second week. On the fifteenth or sixteenth day after section of sympathetic fibers a maximal responsiveness is reached and thereafter is maintained. An important consideration related to sensitization to adrenine is the

fact that severance of preganglionic fibers, according to Hampel, results in only approximately half as great sensitiveness to adrenine as that produced by severance of postganglionic fibers. Similar observations, but on blood vessels, have recently been reported by Aseroft.<sup>11</sup> He estimated that after postganglionic section the vessels are about ten times as sensitive as are the controls, and after preganglionic section only three times as sensitive. Attention to this point allows smooth muscle to be separated from the central nervous influences without being rendered especially responsive—a practical matter, the value of which surgeons have recognized.

The importance of sensitization of vascular smooth muscle to circulated adrenine lies in the fact that common conditions in daily life naturally result in a discharge of an extra amount of adrenine into the circulation. This is due to the control exercised by the sympathetic nervous system on the adrenal medulla. In a long series of experiments, carried on for many years in the Harvard Physiological Laboratory, evidence has been secured that emotional excitement, hypoglycemia, cold, pain, and vigorous muscular activity all increase medullary adrenal secretion.<sup>12</sup> These observations have been confirmed by various investigators using a variety of methods and working independently in different parts of the world. The question naturally arises as to whether the tone of blood vessels deprived of sympathetic nerves will be altered by conditions which influence secretion of adrenine.

First, let it be understood that in man, just as in the cat, as Freeman, Smithwick, and White<sup>13</sup> found, smooth muscle—that of the blood vessels of the fingers, for example—becomes more sensitive to injected adrenalin six to eight days after sympathectomy. In this relation it is of considerable interest that the conditions which have been shown to cause an increase of adrenal secretion are precisely the conditions which may affect contraction of sensitized denervated vessels. Thus, contraction of the blood vessels of the sympathectomized ear of the rabbit has been reported by Grant,<sup>14</sup> who charted the fall of temperature of the ear when a leg was held and the animal struggled. Analogously, Grant and Pearson (Grant<sup>14</sup>) have noted that, when a man struggled against resistance for a minute, there was contraction of his denervated blood vessels, indicated by a fall of temperature of the foot through 2° C. Furthermore, Freeman, Smithwick, and White observed that, when a patient became excited, there was a contraction of the denervated vessels. During insulin hypoglycemia, also, there was a striking vasoconstriction. Chilling of the body, which we know induces sympatho-adrenal activity, as shown by gooseflesh, will also cause a narrowing of the denervated vessels, as Freeman<sup>15</sup> has shown. This contraction is not due to direct action on the sensitized vessels, for it appeared when the hands were maintained at a constant temperature while ice bags were applied to both supraclavicular regions. In all these observations on man the experimental

observations on lower animals have been repeated. They definitely offer evidence that excitement, hypoglycemia, cold, and muscular effort cause effective secretion from the human adrenal medulla. Pain would probably have the same influence, though observations on that point have not been made on man. This result of conditions which increase medulliadrenal secretion probably explains anomalies which not infrequently have been reported regarding the return of spasm in peripheral vessels long after they have been deprived of their sympathetic nerve supply.

In the foregoing account the contraction of denervated blood vessels has been attributed solely to adrenal secretion. There is another agent which may have similar effects. That is the substance "sympathin," which is given off at sympathetic nerve endings when there is a discharge of impulses into the effectors. In 1935 Grant<sup>14</sup> reported that after removal of the adrenal glands or the pituitary body the previous reactions of the normal and the denervated ear were not altered. He presented no record of the changes in the denervated ear when the animal was exposed to a reduced temperature, or was made to struggle, after the adrenals had been extirpated, but presumably those tests were applied. Grant admits the possibility that the sensitive vessels were affected by circulating sympathin. It seems probable that this is the explanation of his observations. We know that denervated vessels become sensitized to sympathin just as they become sensitized to adrenine. And White, Okelberry, and Whitelaw<sup>15</sup> have noted an intense blanching of a rabbit's sympathetomized ear when, after removal of the adrenals, they stimulated hepatic nerves—a mode of liberating sympathin which is highly effective. We have learned that sympathin is discharged into the blood stream under the same conditions as adrenine and that ordinarily sympathin and adrenine collaborate in producing changes in sympathetic effectors. It is quite possible, however, that sympathin may alone produce these changes.

The fact that activity of the sympathetic system provokes a discharge of both sympathin and adrenine and that these two agents can work together to influence regions which have been deprived of their sympathetic nerves<sup>17</sup> raises the question as to whether the recovery of tone in vascular smooth muscle may not be due to the continued presence of a small amount of these substances in the blood stream. According to Satake, Sugawara, and Watanabe,<sup>18</sup> there is a discharge of adrenine from the adrenal medulla, even in the most quiet conditions, amounting to 0.00007 milligram per kilogram of body weight per minute. There is a bare possibility that this extremely small amount may have been due to the manipulation incident to taking the blood sample required for the estimate, though great care was used to avoid disturbance of the animal. In experiments on cats with denervated hearts I was

unable to find any difference between the heart rate in the animals completely at rest and with intact adrenals, and the same animals after the adrenal glands were rendered wholly inactive. Since the denervated heart is an extraordinarily sensitive indicator of adrenal secretion it would appear that the amount of adrenine produced in complete rest is probably not enough to have any influence on vascular tone.

Whether there is another gland of internal secretion—for example, the posterior lobe of the pituitary or the adrenal cortex—which supplies a chemical agent that might account for the restoration of tone in sympathectomized vessels is not known. Certainly if endocrine organs are effective agents in reestablishing the tonic state they are not called into action by the discharge of impulses through sympathetic pathways, for in completely sympathectomized animals those pathways are absent. There is no indication, however, that any gland of internal secretion is necessary for the development of tone in smooth muscle—certainly not the adrenal medulla. That statement is supported by observations on the alimentary tract. Many years ago I isolated the stomach from the central nervous system.<sup>19</sup> The smooth muscle of this organ is *relaxed*, not contracted, by adrenine. And yet, after a short time, the denervated muscle of the gastric wall shows an almost incredible degree of tonic contraction. Until definite proof that an external agent operates to restore “tone” in denervated vascular muscle I believe we are warranted in assuming that the restoration results from an intrinsic property of the muscle itself.

In connection with variations of tone of denervated blood vessels, the interesting reports from Freeman, and Freeman and Zeller on the effects of heat and cold on the circulation rate may be mentioned. In observations on patients Freeman<sup>15</sup> found a remarkably close relationship between the volume flow of blood in a sympathectomized hand and the metabolic rate. When the rate was increased or decreased by placing the hand in warm or cold water the volume flow was correspondingly altered. In unpublished observations Freeman and Zeller have confirmed these data in experiments on totally denervated paws of unanesthetized trained dogs in which one adrenal had been removed and the other denervated. Again the circulation varied with the temperature of the bath in which the paw was immersed. The conclusion was drawn that the blood supply through regions deprived of vasomotor control might be determined by the metabolic needs of the tissues. Although not denying that possibility and deferring until later a consideration of the way in which metabolites may influence blood flow, I may mention that Freeman has recognized that smooth muscle contracts when exposed to cold and relaxes when exposed to warm surroundings, and that therefore the variations in blood flow which he observed might be the consequence of temperature changes in the vessels themselves.

## ADAPTATION OF VASCULAR TONE TO LOCAL NEEDS

The evidence relative to changes of vascular tone in accordance with the quiescence or the activity of organs has been derived chiefly from studies on muscle. The classic experiments of Krogh<sup>20</sup> showed that when the muscles of a guinea pig are made to contract the number of capillaries which are visibly relaxed and containing blood may be more than ten times the number visible in the resting muscle, and in the frog the increase may be nearly fortyfold. The early observations by Chauveau and Kaufmann (see Kaufmann<sup>21</sup>) revealed an increased blood flow through rhythmically active muscles which might be as much as five times the amount passing through the same muscles when at rest. These results have been confirmed by other investigators, notably by Barcroft and Kato<sup>22</sup> who pointed out that the increase occurred as an aftereffect of contraction.

The most recent and apparently the most reliable studies of this phenomenon are those of Anrep,<sup>23</sup> who used a hot-wire anemometer to record the blood flow. By means of this device he was able to show that a tetanic contraction, whether reflex or induced by stimulation of a motor nerve, causes the flow through the muscle to be greatly reduced and may actually stop it. After the contraction, however, it is much increased. If the muscle contracts rhythmically the flow becomes gradually more ample between successive contractions until a maximum is reached. The greater supply of blood depends upon the strength of the contraction. It would appear that the observation, well known since the report by Roy and Brown<sup>24</sup> nearly sixty years ago, that arrest of the circulation is followed by a considerably augmented flow through vessels in which the flow has been checked, may be a phenomenon similar to that seen in active muscles. The phenomenon noted by Anrep, however, is not solely due to a check on the circulation during the contractile phase, for he found that if blood is forced through muscles during their contraction it acquires the property of causing a reduction of vascular tone. Obviously some agent is produced by the activity of the muscle itself that has the observed effect.

For our present interests the question that becomes prominent is that of explaining the increased circulation when skeletal muscle fibers contract and shut off their own blood supply and simultaneously become the seat of special metabolic processes. Various explanations have been given to account for the dilation of blood vessels in active organs. The demonstration by Gaskell<sup>25</sup> that lactic acid lessens the tone of blood vessels, and Bayliss<sup>26</sup> testimony that carbon dioxide has the same effect, serve to bring acid metabolites into the picture as possible agents inducing the larger flow. Whether the observation that lack of oxygen (cf. <sup>24</sup>) has a similar influence is to be ascribed directly to that condition or indirectly to the development of an acid reaction is not yet clear. As Anrep has remarked, there has been a tendency, as each new substance

has been discovered, to ascribe to it responsibility for the vasodilator effect in active muscle and in other organs. Histamine, acetylcholine, adenylic compounds and other unidentified substances have in turn been regarded as the cause of the phenomenon. Gaddum<sup>27</sup> has declared that no single substance known to be present in the tissues could account completely for the characteristics of reactive hyperemia, during which there is a dilation of all the vessels. Liberation of histamine could explain dilation of the capillaries but not dilation of the arterioles—the presence of some other agent would have to be assumed to account for effects on these structures. Possibly the early testimony of Gaskell and Bayliss regarding the action of acids may be most pertinent, for Rous and Drury<sup>28</sup> have shown by direct observation a considerable local increase in the hydrogen ion concentration in ischemic tissues—an increase which under certain conditions might control the blood flow. It is unfortunate that we have no decisive evidence regarding the agencies which adapt the tone of the blood vessels, and thereby the flow of the blood, to the needs of organs as they vary between rest and activity.

#### THE QUESTION OF INHIBITORS OF VASCULAR TONE

##### (I.E., VASODILATOR NERVES)

In discussing inhibition of vascular tone I am not concerned with the depression of activity of the vasoconstrictor center, but instead I wish to take up the pros and cons of the existence of a vasodilator center which produces vasodilation by relaxing smooth muscle. That smooth muscle may be relaxed by nerve stimulation is common knowledge. The relaxation of the stomach and intestines, and likewise the nonpregnant uterus of the cat, when sympathetic impulses are delivered, are noteworthy instances. It would not be strange, therefore, to find nerve impulses which would relax the smooth muscle of blood vessels by inhibiting their tonic state. Nevertheless, Barcroft<sup>29</sup> has argued that the dilation of the blood vessels of the submaxillary gland, for example, when the chorda tympani is stimulated, is due to the action of metabolites set free from the gland and therefore “the hypothesis of dilator fibers in the chorda of the cat seems superfluous.” That argument cannot hold, however, in the effects of stimulating the *nervi erigentes* where metabolites are not produced which could dilate the vessels.

The interest of the Harvard Physiological Laboratory in vasodilator nerves was stimulated by the remarkable behavior of sympathectomized cats. The observation was repeatedly made that if these sympathectomized animals engaged in any vigorous activity they promptly collapsed. When Freeman and Rosenblueth<sup>30</sup> measured blood pressure at the time of a vigorous struggle the fact appeared that the pressure instead of rising, as it does in normal animals, actually fell. Similar observations have been made on dogs. For a period of some days after



the completion of sympathectomy Freeman<sup>31</sup> found that there was so great a drop of pressure when an animal was vigorously exercised that fainting occurred. Later the dog recovers and is able to endure strenuous muscular exertion without the disturbing effects seen in the cat.<sup>32</sup> Nevertheless, as Pinkston, Partington, and Rosenblueth<sup>33</sup> have demonstrated, muscular activity causes some fall of blood pressure even in the dog well recovered from the operation of sympathectomy.

The observations just described have been given different interpretations. Bacq, Brouha, and Heymans<sup>7</sup> have claimed that the fall of pressure is due to muscular metabolites which, as we have seen, are capable of causing a dilation of the blood vessels. In support of this view they found that the addition of carbon dioxide to the air breathed by a sympathectomized cat caused a fall of arterial pressure. It also caused, however, a greatly increased respiratory rate, and the possibility exists, therefore, that the changed conditions brought about by excessive respiration might have produced the effect. Furthermore, there is chance that the excess of carbon dioxide might stimulate a vasodilator center and thereby induce a fall of pressure. It would appear reasonable also that if muscular metabolites are the essential cause of a lowered pressure in sympathectomized animals the dog might be expected to suffer as much as the cat. The effect, though present in the dog, is not so striking as in the cat. The difference between the two species may be attributed to a greater efficacy of vasodilator nerves in the cat. Furthermore, the fall of blood pressure in sympathectomized, vagotomized animals when they struggle starts almost immediately—apparently much too soon to be readily explained by the metabolites resulting from muscular contraction. Also, when the peripheral end of the cut sciatic nerve is stimulated in a sympathectomized cat there is first a rise of blood pressure, as might be expected from Anrep's observations on the effects of muscular contraction, and a fall occurs only after the stimulus ceases. Neither in the cat nor in the dog is struggle associated with this initial rise of pressure. From all these lines of evidence it seems clear that the explanation of the drop in the blood pressure record is not well explained by the development of metabolites alone.

Bacq, Brouha, and Heymans have suggested that there may be non-sympathetic vasoconstrictor nerves and that the fall of pressure in animals deprived of the sympathetic system may result from a block of constrictor impulses. The evidence cited by them was based on the effect of one milligram of percaïn, injected into the spinal canal in the cervical region. This drug, they assumed, produced a "physiological section" of the spinal cord. The consequent drop of arterial pressure they attributed to the action of the drug in eliminating tonic vasoconstrictor impulses. When, instead of using a drug, however, Rosenblueth and I<sup>34</sup> made a true section of the cord in the cervical region and found that it did not modify the pressure of sympathectomized cats, we felt

justified in dismissing as inconclusive the evidence obtained by the Belgian investigators. Our view was confirmed by the observations of Wilson, Roome, and Grimson,<sup>8</sup> and also of Bradshaw<sup>35</sup> that novocaine spinal anesthesia, which dropped the blood pressure of normal animals, had no hypotensive influence on the sympathectomized. Another argument in favor of nonsympathetic vasoconstrictors, which was advanced by Bacq, Brouha, and Heymans, was based on the observation that hypotension in the carotid sinus caused arterial hypertension in the sympathectomized animal. This observation was not confirmed by Thomas and Brooks,<sup>36</sup> however, and likewise not confirmed by Pinkston, Partington, and Rosenblueth.<sup>33</sup> The main reason for giving credit to this accumulation of negative evidence is that Bacq, Brouha, and Heymans do not mention excluding the possibility of regrowth of nerves to the celiac ganglion and the adrenals. As was shown by Bacq and Dworkin,<sup>37</sup> such regrowth may occur, and unless scrupulous care is given to this possibility it may lead to highly confusing results. The weight of evidence favors the view that nonsympathetic nervous influences on the blood vessels are not of vasoconstrictor type.

That it is possible to obtain true vasodilation, i.e., relaxation of vascular tone, in sympathectomized animals by nervous influences acting directly on the vessels, was shown by Rosenblueth and myself<sup>34</sup> in 1934. We made use of Ranson and Billingsley's observation<sup>38</sup> that there are on each side of the floor of the fourth ventricle two well-separated points, stimulation of which causes alteration of blood pressure—the anterior points causing a rise and the posterior a fall. In sympathectomized animals we found that stimulation of the depressor points consistently elicited a fall of blood pressure. We were careful to place the electrodes properly and use threshold stimuli so that there was no attendant muscular movement. The depressor effect was not eliminated by the exclusion of the splanchnic area, for it persisted after the aorta was clamped at the level of the diaphragm. Stimulation of neighboring regions, including the pressor points, did not alter the arterial pressure unless the current was sufficient to induce muscular activity. Then there was an initial rise succeeded by a fall just as when a peripheral nerve is excited.

The experiments of Pinkston, Partington, and Rosenblueth,<sup>33</sup> moreover, brought forth definite evidence that in both the sympathectomized dog and the cat central stimulation of vagus and depressor nerves would cause a distinct fall of blood pressure. In all cases there were no changes of activity except in respiration; and the respiratory change was definitely ruled out as the occasion for the depressor effect. In the sympathectomized cat central stimulation of the brachial nerve, for example, repeatedly produced striking drops of the pressure level. Muscular movements which might be induced by spinal reflexes were eliminated in some instances by section of the efferent nerves which were

involved. These sections altered slightly the magnitude but not the downward direction of the blood pressure response. The results, noted in the sympathectomized cat, were obtained also in experiments on sympathectomized dogs.

The existence of a vasodilator center, the activity of which is reciprocally related to a vasoconstrictor center, was inferred by Bayliss<sup>39</sup> in 1908, for he found that when constrictor impulses were eliminated from a given vascular region by severing its sympathetic fibers, reflexes which involved vasodilation were still effective in causing an enlargement of these sympathectomized vessels. Earlier, Bayliss<sup>2</sup> had reported experiments which revealed the possibility of vasodilator influences in the limbs that might be mediated through the dorsal roots. The phenomena observed in 1913 by Fofanow and Tschalusow<sup>40</sup> and later by Bishop, Heinbecker, and O'Leary<sup>41</sup> and also by Tournade and Malméjac,<sup>42</sup> showed that the vasodilator fibers of the dorsal roots could be activated reflexly. It seems probable, therefore, that in sympathectomized animals these are the efferent pathways of the impulses which cause an inhibition of peripheral tone. They would be, then, responsible for that drop of blood pressure which attends struggle, which follows stimulation of depressor points in the floor of the fourth ventricle, and which results reflexly when afferent nerves are excited.

#### CONDITIONS PRODUCING EXCESSIVE VASCULAR TONE

As is well recognized, the height of arterial pressure depends upon the energy of the output from the heart as related to the resistance to the onward passage of blood into the capillaries. A condition of hypertension, other things equal, depends chiefly on the resistance offered to the blood flow in the finer divisions of the arteries, the arterioles. In such circumstances, with a marked vasoconstriction in that part of the circulatory system, a heightened blood pressure will result. The persistent state of hypertension which develops pathologically in certain individuals presents an important physiological and medical problem. Unfortunately the condition may become so severe—the pressure may rise so high—that life may be endangered; then the adjective “malignant,” applied to it, is fully justified.

Three explanations of the hypertensive state in the arterioles could theoretically be possible. It might result from excessive discharge of vasoconstrictor impulses from the central nervous system, such as to induce an abnormal narrowing of the channels. Or it might be due to increased sensitiveness of the smooth muscle of the arterioles to natural stimuli which cause contraction. Or these small vessels might be pathologically constricted because of direct action upon them of unusual chemical agents. We now have, in fact, evidence that each of these conditions may produce an augmented vascular contraction. We shall consider them in the order mentioned.

1. The studies of Heymans and his collaborators have furnished evidence that if all the restraining nerves are severed—the cardio-aortic nerves (depressor) and those of the carotid sinus as well—there develops a hypertension which persists for an indefinite period. Heymans and Bouekaert<sup>43</sup> have reported long-continued observations on a single animal, a dog. Before section of the restraining nerves the arterial pressure was approximately 140 mm. Hg, and the cardiac rate 90 beats a minute. After section of these nerves the pressure rose promptly to 240 mm. Hg, and thereafter went up gradually until after eight months it reached 300 mm. The heart rate likewise rose until it ran about 300 beats a minute. After sixteen months, when the arterial pressure was about 270 mm. Hg, the abdominal sympathetic strands as well as the splanchnic nerves were severed. Arterial pressure, after being reduced for some days immediately after the operation, stabilized between 280 and 300 mm., i.e., there was no improvement. The heart, however, which had begun to beat more slowly, continued toward the previous normal level.

About the twenty-fifth month, i.e., after two years of high pressure, the celiac plexus was removed. Then there was a marked and lasting fall of the pressure which stabilized at about 200 mm. Hg. It may be that there had been a regrowth of splanchnic (preganglionic) fibers into the celiac ganglion—a possibility already noted—and that the persistence of high pressure was partly due to that. On the other hand, the rise, a short time after excision of the abdominal sympathetic strands and section of the splanchnics, might be explained as a consequence, to some degree, of independent activity of the outlying neurones in the sympathetic system, i.e., those of the prevertebral ganglia. That explanation would be in harmony with the observations of Govaerts,<sup>44</sup> whose experiments indicated that the stellate ganglion, disconnected from the central nervous system, becomes after some days independently active and the source of a cardio-accelerator tone.

The dog studied by Heymans and Bouekaert did not have a restoration of normal pressure until both thoracic sympathetic chains were removed, in addition to the removal of the abdominal chains. When these final operations were completed, after 27 months, the arterial pressure was restored to its former level. The Belgian investigators have drawn the conclusion that when hypertension is brought about by removal of the restraining nerves the consequent persistently high arterial pressure is abolished only when there is complete removal of the sympathetic strands, and, in addition, an excision of isolated sympathetic ganglia such as the celiac. They especially emphasize the possibility that these ganglia, even when disconnected from the central nervous system, may become centers of vasoconstrictor tone. Unfortunately their conclusions are based on a single experiment, and that one not critically performed.

The experiment is, however, of the sort which should be performed. Because of the importance of the inferences drawn from it, it should be carefully repeated.

2. That some blood vessels, even though innervated, may become especially sensitive to natural stimuli was shown by Lewis<sup>45</sup> and by Heinbecker and Bishop,<sup>46</sup> in studies on patients with Raynaud's disease. Lewis noted that when cold was locally applied to an affected finger there was local vasospasm without general involvement of the sympathetic system. And Heinbecker and Bishop observed that adrenine, whether subcutaneously injected or secreted in response to hypoglycemia, produced exceptionally emphatic constriction in the vessels of abnormal digits. They also adduced evidence that these vessels were peculiarly overresponsive to normal sympathetic impulses; since these impulses liberate sympathin, however, and that substance closely resembles adrenine, the effect is what might be expected.

In all these cases the disease had reached an advanced stage. White,<sup>47</sup> (p. 163) has presented arguments which would attribute the phenomenon of local sensitiveness to the pathology which develops at that stage and would explain the early appearance of spasm in Raynaud's disorder to hyperactivity of vasoconstrictor nerves.

3. The third way in which dangerous vasoconstriction might develop is through peripheral stimulation of the smooth muscle of the arterioles by unusual chemical agents. Naturally one thinks, first, of such natural agents as pituitrin and adrenine, both of which are capable of causing contraction of smooth muscle. In acute experiments, however, pituitrin does not have a persistent effect in contracting vascular muscle—successive doses become less effective than the first. Furthermore, Grant has shown that vascular tone develops in the absence of the pituitary gland. Since we have experimental proof that the adrenal medulla does not secrete unless it is stimulated by nervous impulses (or in the rare condition of extreme asphyxia), the idea that secreted adrenine plays a rôle in producing excessive constriction of the arterioles must, I believe, be abandoned.

The most illuminating indication that persistent hypertension is induced by some chemical agent, apparently other than that put forth by one or more of the glands of internal secretion, has come from the important experiments of Goldblatt and his collaborators.<sup>48</sup> I hesitate to expound the evidence developed from these experiments because a paper which is to be given this afternoon will clearly bring out the facts. The most interesting point in relation to the present discussion, however, is that Freeman and Page have been able to demonstrate that reduction of the blood flow through the kidneys by application of Goldblatt's clips causes hypertension in animals which have been completely sympathectomized. Or if hypertension has been produced by partial ischemia of the kidneys, subsequent sympathectomy does not improve the situation. These observations appear to place the action in some

agent which affects vessels at the periphery. There is, however, the bare possibility that the hypothetical agent might influence primarily pre-vertebral ganglia such as the celiac and the inferior mesenteric, and by exciting these isolated groups of cells, which constrict the splanchnic vessels, might be the occasion of the hypertensive state.

We have now surveyed briefly recent studies on the effects of sympathectomy on vascular tone, the conditions which affect vascular tone after sympathectomy, the adaptation of vascular tone to local needs of the tissues, the question of inhibitors of the tonic state in blood vessels, and the conditions which may produce excessive vasoconstriction. Unfortunately time has not been available for discussion of the factors which influence specifically the functional adjustments of the capillaries. That subject will remain for some future lecturer to consider, who comes before you to refresh the memory of George E. Brown, and his services to the physiology and pathology of the circulatory system.

## REFERENCES

1. Stricker, S.: Untersuchungen über die Gefässnervenzurzel des Ischiadicus, Sitzungsber. d. k. Akad. d. Wissensch. Math.-naturw. kl. Wien 74: 173, 1876.
2. Bayliss, W. M.: On the Origin From the Spinal Cord of the Vaso-dilator Fibres of the Hind-Limb and on the Nature of These Fibres, *J. Physiol.* 26: 173, 1901. And, Further Researches on Antidromic Nerve Impulses, *Ibid.* 28: 276, 1902.
3. Goltz, Fr.: Über gefässweiternde Nerven, *Arch. f. d. ges. Physiol.* 9: 174, 1874.
4. Dale, H. H., and A. N. Richards: The Vaso-dilator Action of Histamine and Some Other Substances, *J. Physiol.* 52: 110, 1918.
5. Grant, R. T., and Bland, E. F.: Observations on the Vessels and Nerves of the Rabbit's Ear With Special Reference to the Reaction to Cold, *Heart* 16: 69, 1932.
6. Cannon, B.: The Effects of Progressive Sympathectomy on Blood Pressure, *Am. J. Physiol.* 97: 592, 1931.
7. Bacq, Z. M., Brouha, L., and Heymans, C.: Reflexes vasomoteurs d'origine sino-carotidienne et actions pharmacologiques chez le chat et chez le chien sympathectomisés, *Arch. internat. de pharmacodyn. et de thérap.* 48: 429, 1934.
8. Wilson, H., Roome, N. W., and Grimson, K.: Observations on Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System in Dogs, *Ann. Surg.* 103: 498, 1936.
9. Meltzer, S. J., and Auer, C. M.: Studies on the "Paradoxical" Pupil-Dilatation Caused by Adrenalin, *Am. J. Physiol.* 11: 28, 1904.
10. Hampel, C. W.: The Effect of Denervation on the Sensitivity to Adrenine of the Smooth Muscle in the Nictitating Membrane of the Cat, *Ibid.* 111: 611, 1935.
11. Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities, *Brit. J. Surg.* 24: 787, 1937.
12. Cannon, W. B.: Bodily Changes in Pain, Hunger, Fear, and Rage, New York, 1929; and the Wisdom of the Body, New York, 1932.
13. Freeman, N. E., Smithwick, R. H., and White, J. C.: The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy, to Adrenalin and to Adrenal Secretion Resulting From Insulin Hypoglycemia, *Am. J. Physiol.* 107: 529, 1934.
14. Grant, R. T.: Further Observations on the Vessels and Nerves of the Rabbit's Ear, With Special Reference to the Effects of Denervation, *Clin. Sc.* 2: 1, 1935.
15. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, *Am. J. Physiol.* 113: 384, 1935.
16. White, J. C., Okelberry, A. M., and Whitelaw, G. P.: Vasomotor Tonus of the Denervated Artery, *Arch. Neurol. & Psychiat.* 36: 1251, 1936.
17. Cannon, W. B., and Rosenblueth, A.: Autonomic Neuro-effector Systems, New York, 1937.

18. Sataké, Y., Sugawara, T., and Watanabé, M.: A Method of Collecting the Blood From the Suprarenal Gland in the Dog, Without Fastening, Nareotizing, Laparotomy, or Provoking Any Pain, *Tohoku J. Exper. Med.* 8: 501, 1927.
19. Cannon, W. B.: The Motor Activities of the Stomach and Small Intestine After Splanchnic and Vagus Section, *Am. J. Physiol.* 17: 429, 1906.
20. Krogh, A.: The Anatomy and Physiology of the Capillaries (revised edition), New Haven, 1929.
21. Kaufmann, M.: Recherches expérimentales sur la circulation dans les muscles en activité physiologique, *Arch. de Physiol.* 24: 279, 1892.
22. Barcroft, J., and Kato, T.: Effects of Functional Activity in Striated Muscle and Submaxillary Gland, *Phil. Trans., Roy. Soc., London*, 207 B: 149, 1916.
23. Anrep, G. V.: Studies in Vascular Regulation, 1936, Stanford Univ. Press.
24. Roy, C. S., and Brown, J. G.: The Blood Pressure and Its Variation in the Arterioles, Capillaries and Smaller Veins, *J. Physiol.* 2: 323, 1879-80.
25. Gaskell, W. H.: Über die Änderung des Blutstroms in den Muskeln durch die Reizung ihrer Nerven, *Arch. a. d. physiol. Anstalt, Leipzig* 11: 45, 1876.
26. Bayliss, W. M.: The Action of Carbon Dioxide on Blood Vessels, *J. Physiol.* 26: 32, 1901.
27. Gaddum, J. H.: Gefäßweiternde Stoffe der Gewebe, Leipzig, 1936.
28. Rous, P., and Drury, D. R.: Outlying Acidosis Due to Functional Ischemia, *J. Exper. Med.* 49: 435, 1929.
29. Barcroft, J.: The Mechanism of Vasodilation in the Cat's Submaxillary Gland, *J. Physiol.* 36: 53, 1908.
30. Freeman, N. E., and Rosenblueth, A.: Reflex Stimulation and Inhibition of Vasodilators in Sympathectomized Animals, *Am. J. Physiol.* 98: 455, 1931.
31. Freeman, N. E.: Personal communication.
32. Brouha, L., Cannon, W. B., and Dill, D. B.: The Heart Rate of the Sympathectomized Dog in Rest and Exercise, *J. Physiol.* 87: 345, 1936.
33. Pinkston, J. O., Partington, P. F., and Rosenblueth, A.: A Further Study of Reflex Changes of Blood Pressure in Completely Sympathectomized Animals, *Am. J. Physiol.* 115: 711, 1936.
34. Rosenblueth, A., and Cannon, W. B.: A Further Study of Vasodilators in Sympathectomized Animals, *Ibid.* 108: 599, 1934.
35. Bradshaw, H. H.: The Fall in Blood Pressure During Spinal Anesthesia, *Ann. of Surg.* 104: 41, 1936.
36. Thomas, C. B., and Brooks, C. M.: The Effect of Sympathectomy on the Vasomotor Carotid Sinus Reflexes of the Cat, *Am. J. Physiol.* 113: 130, 1935.
37. Baer, Z. M., and Dworkin, S.: Regeneration of Fibers in the Sympathico-Adrenal System, *Ibid.* 93: 629, 1930.
38. Ranson, S. W., and Billingsley, P. R.: Vasomotor Reactions From Stimulation of the Floor of the Fourth Ventricle, *Ibid.* 41: 85, 1916.
39. Bayliss, W. M.: On Reciprocal Innervation in Vasomotor Reflexes and on the Action of Strychnine and Chloroform Thereon, *Proc. Roy. Soc., London*, 80 B: 339, 1908.
40. Fofanow, L. L., and Tschalussow, M. A.: Über die Beziehungen des N. depressor zu den vasomotorischen Zentren, *Arch. f. d. ges. Physiol.* 151: 543, 1913.
41. Bishop, G. H., Heinbecker, P., and O'Leary, J. L.: The Function of the Non-myelinated Fibers of the Dorsal Roots, *Am. J. Physiol.* 106: 647, 1933.
42. Tournade, A., and Malméjac, J.: Mécanisme du réflexe vaso-dilatateur que provoque l'excitation du nerf de Hering, *Compt. rend. Soc. de Biol.* 112: 679, 1933.
43. Heymans, C., and Bonekaert, J. J.: Hypertension artérielle chronique expérimentale et sympathectomie, *Bull. Acad. roy. de méd. de Belgique*, Feb. 29, p. 42, 1936.
44. Govaerts, J.: Apparition d'un tonus cardio-accélérateur dans le ganglion stellaire déconnecté centralement, *Compt. rend. Soc. de Biol.* 119: 1181, 1935.
45. Lewis, T.: Experiments Relating to the Peripheral Mechanism Involved in Spasmodic Arrest of the Circulation in the Fingers, a Variety of Raynaud's Disease, *Heart* 15: 7, 1929.
46. Heinbecker, P., and Bishop, G. H.: On the Mechanism of Spastic Vascular Disease, *Proc. Soc. Exper. Biol. & Med.* 32: 152, 1934.
47. White, J. C.: The Autonomic Nervous System, New York, 1935.
48. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* 59: 347, 1934.

## STUDIES IN THE PATHOLOGY OF VASCULAR DISEASE\*

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**E**VIDENCE concerning the basic processes leading to the formation of atheroma and related vascular changes is presented. This evidence has been obtained by combination and intensive application of known techniques. It is believed the new knowledge aids in the understanding of the anatomical processes involved in atherosclerosis and that this points the way to further study of cause as well as relation of vascular and organ changes in a group of diseases.

The importance of vascular disease in its various manifestations need not be stressed. As a result of rapidly increasing knowledge of diseases of childhood and early maturity and improved measures for their prevention and care, vascular disease and associated organic changes now top the mortality list. Contributions concerning the pathology of the various processes have been disappointing. The etiology is obscure, and the source of the materials, lipid and otherwise, so characteristic of early atheroma is no clearer, despite many attempts to relate them to diverse maladjustments, especially dietary.

Present-day descriptions of the process differ in no essential from those of Morgagni save that they are more brief and employ a somewhat changed nomenclature. The histological picture and its interpretation is not different from that of the time of Virchow. The description of the typical atheroma, as given in contemporary texts, briefly, is somewhat as follows: The intimal thickening, gray, waxy, or yellow and opaque, bulges into and partially or completely occludes the lumen of the vessel. As the patch, devoid of any vascularity, grows, its deeper part near the media undergoes necrosis since it is far removed from the circulating blood in the lumen, and insulated from the vasa in the adventitia by the media. If this necrosis extends to the surface and involves the endothelium, an atheromatous ulcer develops, with thrombus formation supervening. Vascularity at the margin of the plaque is described by some but not emphasized, for the healthy vessel wall has not been shown to have its own blood-carrying channels except in the adventitia and outer half of the media, and no implication of such channels playing any significant rôle in the manifestation of atherosclerosis

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Aided by grants from the Josiah Macy, Jr., Foundation and the Research Funds of the Yale University School of Medicine.

Read before The American Heart Association, June 7, 1937, in Atlantic City, N. J.



has been forthcoming. They have been stressed in syphilis and also in rheumatic fever, but these have been regarded as specific types of lesions and not pertinent in any consideration of atherosclerosis.

The methods adopted for this study involve the clearing of tissues by well-known means to increase their translucency. The principles involved require no elaboration; the optical nature of the clearing agent as well as its solvent or other action on the tissues plays a rôle in the effectiveness of the whole process. In addition, the removal of mineral deposits by decalcification either prior to clearing or after, with re-clearing in the latter event, is an invaluable aid, bringing to view hitherto undiscovered channels which are then available for gross or micro-injection with the aid of the dissecting microscope. The latter is an indispensable equipment, allowing the clearing processes to be followed closely, and facilitating dissection of the various coats of an artery.

It has been possible to demonstrate a remarkably extensive pattern of circulation in the aorta of the cow. When the vessel is injected with India ink from the proximal end, with the branches and distal end ligated, the adventitial circulation becomes evident at once. These vessels in the cleared specimen are seen to penetrate the media for a great distance and at times actually to connect with the lumen of the vessel through very small orifices. When the aorta is opened and a wide-mouthed cannula connected with an injection apparatus is placed over the mouth of a branch, small vessels arising from the lip of the mouth of the branch become conspicuous. These course under the intima and anastomose freely with the above described adventitial vessels and with the branches of the minute vessels which arise independently from the lumen of the aorta. When the injection cannula is placed over such a minute orifice, this vessel may be injected independently. The rami of vessels arising from these several sources: (1) the adventitia, (2) the mouths of branches, (3) independent orifices, anastomose freely in the wall of the aorta of the cow. This pattern is demonstrable to a variable extent in the vessels of several species of animals.

The developmental basis for such a vascular pattern has been laid by the careful investigations of Bremer.<sup>1</sup> The pattern is demonstrated with facility in the veins of man, and it is unnecessary to do more than direct attention to the heart—an adapted vessel with its coronary and so-called thebesian circulation as described recently by Wearn and his associates<sup>2</sup>—to realize that it would not be remarkable if a similar pattern were demonstrable in the arterial wall of man. That this pattern is difficult to show in its entirety in all human arteries is undeniable. Frequently, however, in the coronaries and in the abdominal aorta very minute vessels are encountered arising independently from the wall and running to the adventitia where they anastomose in the rich adventitial

plexus. Occasionally such vessels, as they penetrate the aorta, are seen to give off small branches to the intima and media. After examination of many human arteries, it must be emphasized that vessels are seldom demonstrable in the intima or in the inner half of the media when no irritative, obliterative, or morbid process is present. The basic pattern becomes clearly visible, however, and often exaggerated in many of the processes that involve the vessel, including, in addition to atherosclerosis, the physiological obliterations as in the ductus arteriosus, and the lengthening and inelasticity associated with senility. Emphasis is laid upon this vascular pattern since in its topographical extent it partially determines the location and nature of the pathological processes.

One of the commoner manifestations of this vascularity is hemorrhage in the wall of blood vessels, occurring in or between any of the several coats, and sharing with the vascular network the safety of relative obscurity until injection and clearing bring both to view. The extent and status of the extravasated blood vary. It occurs as scattered well-preserved free cells, as phagocytized particles in the monocyte and as a residue of iron, demonstrable with Turnbull's well-known Prussian blue reaction. It is found in the grossly opaque yellow linear patches encountered in the aorta, often in young people dying of acute disease. It is found again as larger bright red, more or less oval masses in the depths of a thickened intima where supposedly there are no vessels. Again the extravasation may be more diffuse, like an ecchymosis. There is every reason to believe that such escaped blood can assume the characteristic forms of hemorrhage in any other tissue, modified only by the physical characteristics of the area in which it finds itself.

Such hemorrhages are encountered with great frequency and are not confined to any vessel or group of vessels. The literature cites instances of adventitial hemorrhages occurring both in man and in animals subject to a number of different diseased states, but as far as is known they are not frequently described in the intima or the media. In a recent publication Paterson,<sup>3</sup> in studying a series of coronary arteries in which thrombosis had occurred, discusses hemorrhage in the intimal tissue and describes small vessels in the intima arising from the lumen.

It is not surprising that many hemorrhages are seen at or near the origin of branches, since the small vasa which so frequently arise from the lips of such branches divide and subdivide to form an extensive plexus about the branch and also extend for some distance in the wall of the artery. These small vessels are seen frequently to be compressed around an oval clot in the wall, to run to the edge of a clot, or to course through areas of extravasated blood. Likewise, small vessels are found which arise from the lumen directly and which can best be described as trees with the bases of their trunks at the surface of the intima, their ramifying branches ornamenting the depth of the intima and every now

and again coming into contact with a hemorrhage. The impression must not be given that vascularity and hemorrhage are always coincidental, for this is not the case. While it is usually possible to demonstrate vascular channels in association with hemorrhage, this is not invariably true, and certainly very extensive vascular channels, even sinusoid-like passages, are found in the thickened intima where no hemorrhage can be seen.

Subsequent changes of the extravasated blood in the intima again reveal unexpected findings. There appears to be a gradual accumulation at the site of the hemorrhage of fatty material which is stainable with sudan III and which frequently contains the so-called "cholesterin clefts," giving the appearance of the classical atheroma. It is reasonable to suppose, therefore, that this fatty material is derived from, and eventually replaces, the blood of the original hemorrhage, a process analogous to the apparent changes observed in hemorrhages in thyroid adenomas and in cavernous hemangiomas. Such a conclusion is borne out by the fact, repeatedly confirmed, that a typical yellow atheromatous plaque may, on careful examination by the methods outlined above, show at its periphery a network of capillaries containing red blood cells and anastomosing, outside the zone of fat and necrosis, with obviously well-delineated and well-functioning blood channels. Often, too, the injection mass will merge with the blood and the cholesterol-containing fatty material of the atheroma. This happens only when the atheroma has softened, as it undoubtedly does at some stage. Evidence to support the statement is encountered when a partially disintegrated, bulging mass that resembles an egg yolk in color is cut with a sharp razor and its viscid content escapes. Naturally when such a focus in the intima extends to and through the endothelial lining of the lumen, it may discharge itself to form an atheromatous ulcer, and in such a cavity fresh blood may accumulate not only from the lumen but also from bleeding vessels in the depths of the crater.

The transformation of the fat-rich necrotic mass into calcified material may take place by a mechanism similar to that described by Klotz, involving saponification of fatty acids to form calcium soaps with subsequent transformation into calcium phosphate and carbonate. On such a basis the form of the ultimate concretion, whether sheetlike or roughly spherical, would depend upon the shape of the original extravasation or perhaps upon another fact, quite the same in principle though dependent upon slightly different physical conditions, which will be described in the following paragraph.

As has been said, the vascular channels may become very conspicuous in the thickened intima. Often they tend to arrange themselves parallel to the lumen of the vessel, and they may be traced from their origin at the intima above the thickening to their exit from the wall below the

thickening, perhaps into the lumen of the same mother vessel or into the large channel of a nearby branch. The impression is obtained that they may act as by-passes or detours when the lumen of the mother vessel is narrowed and even obliterated. The similarity of this intramural pattern to that of extramural adventitial collaterals, so strikingly depicted by Luigi Porta<sup>4</sup> as long ago as 1845 after experimental ligation of arteries, sustains this interpretation. The pattern may become very intricate, and the differentiation between it and the complex canalization of thrombi may become very difficult, if not impossible. This phase will not be dealt with now. Attention is drawn to these intramural channels, which are often larger than the narrowed lumen of the original vessel, because they are subject to great variations in length and width, and despite the free anastomoses that they frequently exhibit may be isolated from the circulation by constriction of their mouths by one or another event. If this happens, the blood in these vessels stagnates, and it is probable that clotting may occur, although evidence for this has not been developed. Blood in such a vessel may go through all the transformations of an extravasation within the vessel wall, as described above. And it may be converted through the fatty stage to stone. This, then is the formation of a "lith" from blood—a second method for the production of calcified masses.

Among the interesting facts encountered none have been more illuminating than those associated with obliteration of the ductus arteriosus. At birth its wall seems quite avascular; within twelve hours, when it may be contracted to partial occlusion, vessels are demonstrable in the wall arising either from the adventitia or the intima. At two months the lumen is more or less occluded by an extremely vascular connective tissue, the vessels of which come from the intima of the pulmonary artery and aorta, as well as from the adventitia of the ductus. They vary in width, and sinusoid-like dilatations are not infrequent. Even at this age opacities and concretions are found in these dilated channels, and in specimens from older individuals more or less calcification is encountered. The entire ductus may be a series of such stones, and they may extend to the subintima of the aorta where a sheet of hard lime may be spread out and may surround the closed orifice of the ductus.

Obviously, the blood encountered so frequently in the walls of the blood vessels can only get there through preexisting channels. "Skimmers" that function to accumulate fluid without formed blood elements have not been demonstrated. The question concerning the nature of the tissue response to the extravasated blood cannot be more than touched upon at this time. The proliferated intimal tissue varies tremendously in the proportion of capillary vessels and connective tissue, as has been frequently demonstrated by both injection and by study of stained sections. This variability may be dependent upon the presence of specific stimuli, as well as upon intrinsic constitutional factors.

## SUMMARY

The above presentation attempts to emphasize the following:

1. The importance of continuity of anatomical study so that topographical relations are clarified rather than lost by higher magnifications.
2. The value of clearing agents and of injection masses in such study.
3. The pattern of mural circulation in the vascular system including the arteries and the veins in man and beasts.
4. Hemorrhage derived from intramural circulation as an important element in the development of atherosclerosis.

## REFERENCES

1. Bremer, J. L.: The Origin of the Renal Artery in Mammals and Its Anomalies, *Am. J. Anat.* 18: 179, 1915.
2. Wearn, J. T., Mettier, S. R., Klumpp, T. G., and Zschiesche, L. J.: The Nature of the Vascular Communications Between the Coronary Arteries and the Chambers of the Heart, *AM. HEART J.* 9: 143, 1933.
3. Paterson, J. C.: Vascularization and Hemorrhage of the Intima of Arteriosclerotic Coronary Arteries, *Arch. Path.* 22: 313, 1936.
4. Porta, Luigi: *Delle alterazioni patologiche delle arterie per la legatura e la torsione*, Milan, 1845.

# HYPERTENSION PRODUCED BY CONSTRICTION OF THE RENAL ARTERY IN SYMPATHECTOMIZED DOGS\*

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**H**YPERTENSION has been consistently produced in experimental animals by compression of the renal artery.<sup>1-4</sup> No entirely satisfactory explanation for the rise in blood pressure has yet been offered. Evidence has been presented that the hypertension occurs in spite of removal of one adrenal and denervation or demedullation of the other.<sup>1</sup> Bilateral splanchnic nerve resection does not alter it<sup>5</sup> nor does section of the anterior spinal nerve roots from sixth thoracic to the second lumbar segments.<sup>21</sup> The renal nerves are not necessary for its development.<sup>2, 3</sup> Since the control of the arterial pressure is chiefly dependent upon the peripheral resistance, the cardiac output and the blood volume, the part played by these physiological mechanisms in the genesis of experimental hypertension was investigated.

## METHODS

Dogs were used in all of our experiments. They ranged in weight from 9 to 15 kilos. The systolic and diastolic blood pressures were taken by the auscultatory method.<sup>3, 6, 7</sup> The bell of the stethoscope measured 2.2 cm. in diameter and was strapped to the anterior medial aspect of the ankle, at or just above the joint. A pneumatic cuff 5 cm. in width and 14 cm. long, encased in a cloth bag 5 by 28 cm. was wound around the leg just above the ankle. The dog was trained to lie on its right side and the pressure taken from the right hind leg. Systolic blood pressure values obtained by the auscultatory method agreed closely with those obtained in two dogs with van Leersum carotid loops.

Hypertension was produced by constriction of the renal arteries, as first described by Goldblatt, Lynch, Hanzal, and Summerville.<sup>1</sup>

Total sympathectomy was performed in three or four stages under amytal (25 mg. per kg.) and intratracheal, positive-pressure, ether anesthesia. The technique employed was similar to that described for cats by Cannon, Newton, Bright, Menkin, and Moore.<sup>8</sup> Care was taken to ensure complete removal of the sympathetic chains. At the first stage of the operation, the right thoracic sympathetic chain was removed from the stellate to the twelfth thoracic ganglion. A black thread or silver clip was attached to the upper end of the right abdominal chain as a

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Read before The American Heart Association, section for the study of the Peripheral Circulation, at Atlantic City, N. J., June 7, 1937.

marker. At the second stage, through an abdominal incision, the right chain was freed from the promontory of the sacrum and was followed up under the diaphragm until the marker was reached. At the same stage, the left abdominal chain was resected from the fifth lumbar ganglion to the diaphragm and a marker was placed on the lower end of the left thoracic chain. At the final stage, the left thoracic chain was followed down from the stellate to the twelfth thoracic ganglion, under the diaphragm, until the marker was located.

Cardiac denervation and thoracic sympathectomy were performed in two stages by the intrathoracic approach. A modification of the technique used in cats, described by Cannon, Lewis, and Britton<sup>9</sup> was employed. Through the fourth right interspace the sympathetic chain was freed from the eighth thoracic ganglion to the stellate ganglion. After the branches of this ganglion to the brachial plexus and intercostal nerves had been severed, the parietal pleura just cephalad to the innominate vein was incised. By blunt dissection the vagus nerve was exposed and the recurrent laryngeal nerve identified in its course around the subclavian artery. The middle cervical ganglion is intimately attached to the vagus approximately at the point at which the recurrent laryngeal nerve leaves the trunk.<sup>10</sup> All branches of the right recurrent nerve were severed and the vagus trunk divided below the point at which the recurrent laryngeal leaves it. The trunk was then again divided below the middle cervical ganglion and after division of one arm of the ansa Vieusseni, the sympathetic chain was removed with the middle cervical ganglion and a segment of the vagus trunk in one piece.

On the left side, an incision was made in the fourth interspace. The stellate ganglion was identified and all the branches divided except one limb of the ansa Vieusseni. This limb was then followed up to the middle cervical ganglion. By sharp and blunt dissection this ganglion was freed from the vagus and was removed with the sympathetic chain to the eighth thoracic ganglion. All branches of the left vagus were cut from the region just above the site of the middle cervical ganglion to the root of the lung. By this operation, all cardiac nerves were severed, while the recurrent laryngeal nerve was saved on the right side. On the left side the main trunk of the vagus was saved to supply the gastrointestinal tract.

The plasma volume was measured by spectrophotometric determination of the disappearance curve of the dye "T-1824" according to the technique of Gregersen, Gibson, and Stead.<sup>11</sup>

#### RESULTS

*A. Sympathetic Vasomotor Control.*—Total sympathectomy did not prevent the development of hypertension from compression of the renal arteries. The result presented in Fig. 1 was confirmed in six other dogs.

\*The dye was obtained through the kindness of Dr. Gregersen.

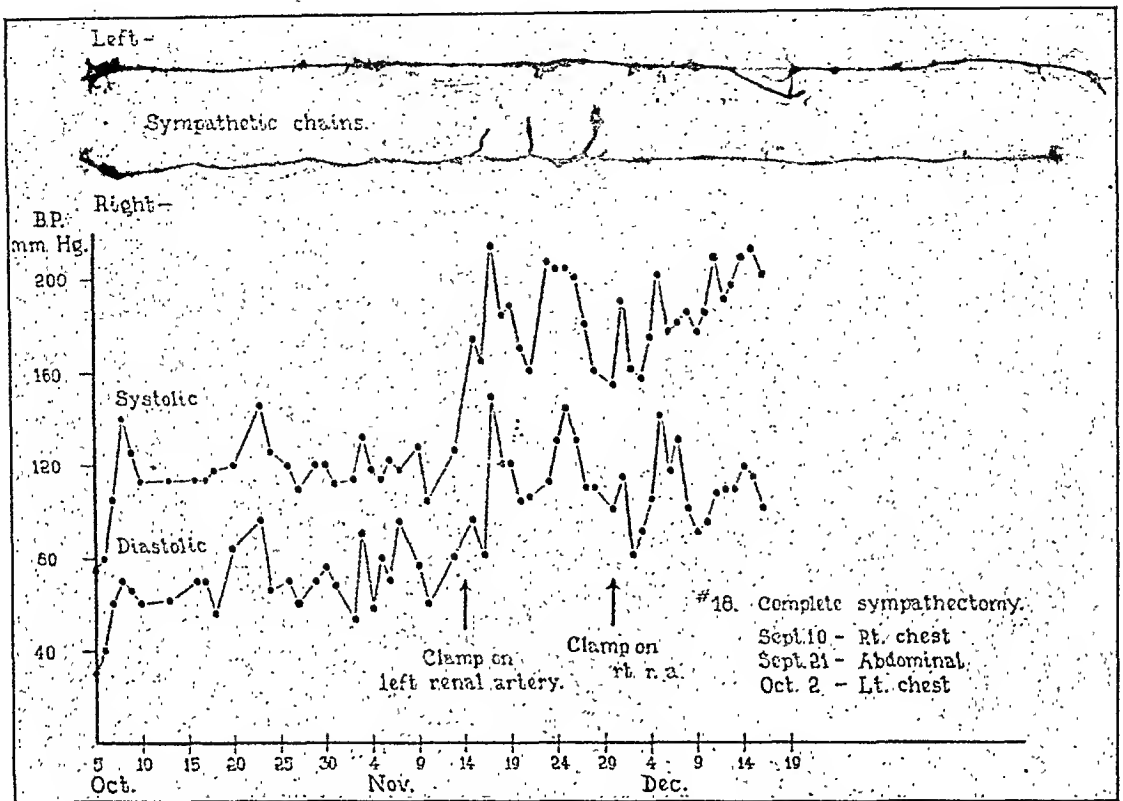


Fig. 1.—Effect of application of Goldblatt clamps to renal arteries on systolic and diastolic blood pressure of sympathectomized dog. The unbroken sympathetic chains are shown above the chart.

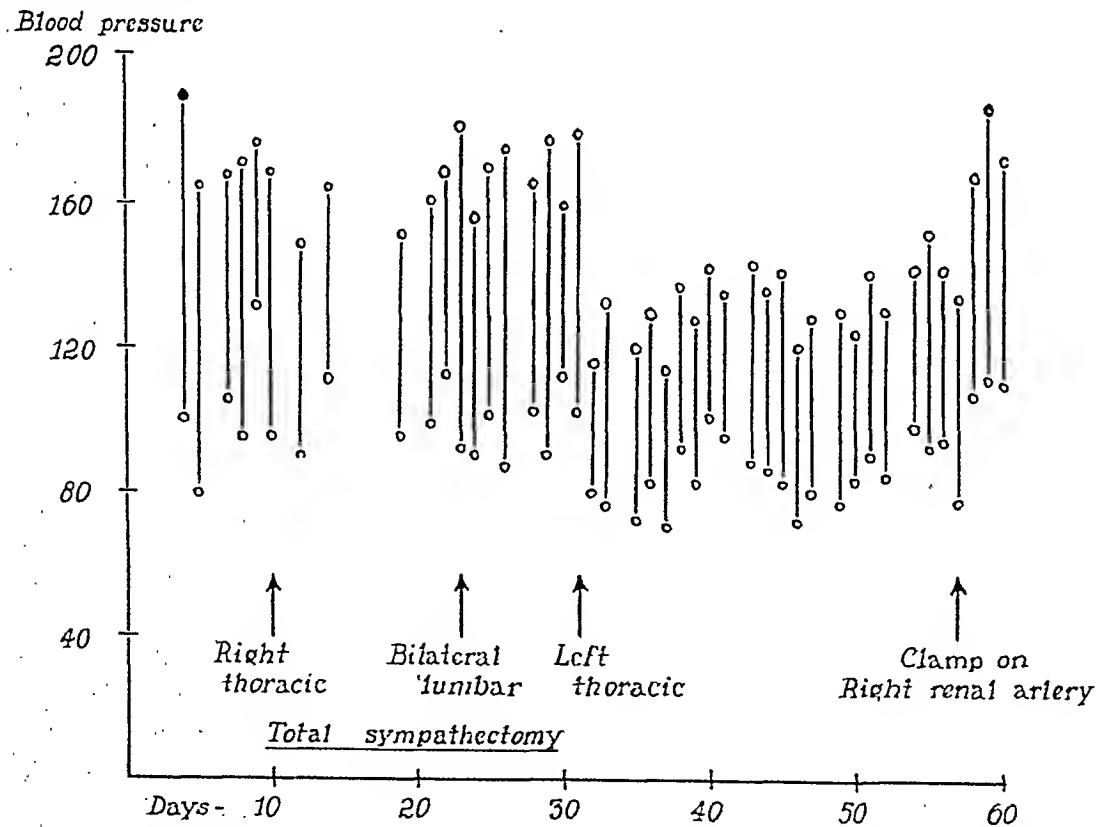


Fig. 2.—Reduction of spontaneous high blood pressure in dog by total sympathectomy. Hypertension then produced by constriction of the right renal artery.



Fig. 2 illustrates the decrease which was produced by sympathectomy in a dog with spontaneous elevation of blood pressure. With the pressure at a normal level following sympathectomy, application of a Goldblatt clamp to the right renal artery caused a prompt increase of the pressure to a hypertensive level.

In contrast to the reduction of blood pressure produced by sympathectomy in the normal dog, with moderate spontaneous elevation of blood pressure, Fig. 3 shows that the hypertension produced by compression of the renal arteries was not materially affected by sympathectomy.

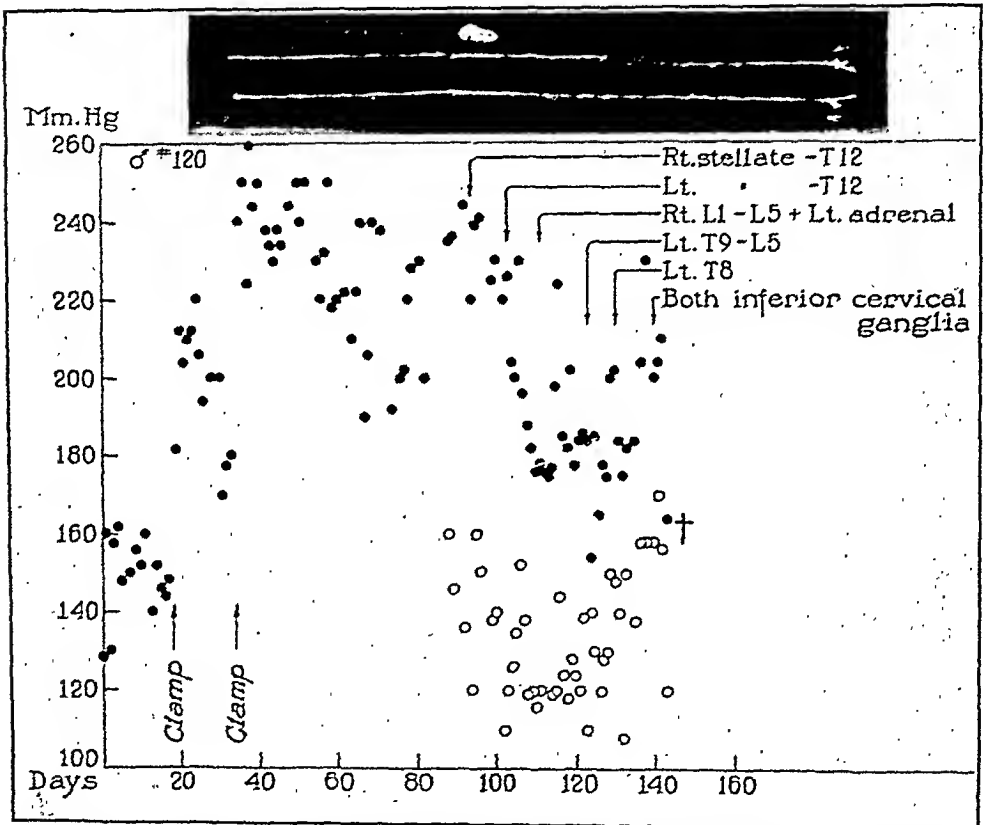


Fig. 3.—Showing that the hypertension produced by compression of the renal arterioles is not materially affected by progressive sympathectomy. A photograph of the two sympathetic chains and the adrenal gland is shown at the top of the chart.

If the elevated blood pressure in the dog made hypertensive by constriction of the renal arteries was the result of increased sympathetic activity, a fall in blood pressure would be expected upon the administration of large doses of ergotamine tartrate.<sup>12</sup> On the contrary, in two dogs, an additional rise was obtained as depicted in Table I. These data are merely suggestive as it was not possible to reverse the pressor effect of 0.3 c.c. of 1:1000 adrenalin (intravenous) by such large doses as 3 mg. of ergotamine tartrate given by vein in unanesthetized hypertensive dogs.

TABLE I

EFFECT OF INTRAVENOUS ADMINISTRATION OF ERGOTAMINE TARTRATE ON BLOOD PRESSURE OF DOG WITH HYPERTENSION FROM COMPRESSION OF THE RENAL ARTERIES

|                                     |                         |
|-------------------------------------|-------------------------|
| Control B.P. level = 210 mm. Hg     |                         |
| <i>1 mg. gynergen intravenously</i> |                         |
| 4 minutes later B.P. =              | 206-216 mm.             |
| 8 minutes later B.P. =              | 230                     |
| 10 minutes later B.P. =             | 240                     |
| 20 minutes later B.P. =             | 216                     |
| 24 hours later B.P. =               | 190-200. Heart rate 86. |
| <i>3 mg. gynergen intravenously</i> |                         |
| 10 minutes later B.P. =             | 240-250. Heart rate 48. |
| 25 minutes later B.P. =             | 230. Vomited.           |

*B. Reflex Cardiac Control.*—Total sympathectomy in the dog does not abolish the power of reflex cardiac acceleration, since cardio-accelerator fibers have been reported to run in the vagus nerves.<sup>13</sup> It was therefore possible that the rise in blood pressure in the sympathectomized dog, after application of clamps to the renal arteries, was due to the reflex cardiac excitation. Fig. 4 shows the rise in heart rate with elevation of blood pressure from the administration of atropine sulfate (0.2 mg. per kilo, intravenously) to the completely sympathectomized dog.

After the heart has been denervated by intrathoracic section of all the cardiac nerves, no acceleration takes place after the administration of atropine. In Fig. 5 are presented parts of the original record taken from one of the four dogs in which cardiac denervation was successfully completed. In none of these animals was hypertension from compression of the renal arteries prevented.

Combined total sympathectomy and cardiac denervation was successfully performed on one hypertensive dog. Even in this animal, as can be seen in Fig. 6, the hypertension was not reduced. A clamp was applied to the left renal artery at the last stage of the total sympathectomy. A slight additional rise in blood pressure was observed after this operation.

After the first two operations, the heart was completely denervated. Acceleration is then chiefly dependent upon the secretion of adrenaline. At the third stage, the right adrenal was denervated by removal of the remainder of the right sympathetic chain. The left adrenal was still normally innervated. It may be seen from the chart (Fig. 6), that the basal heart rate over the week preceding the final stage varied between 92 and 104 beats per minute. After the fourth operation, when the remaining adrenal was denervated by removal of the remainder of the left sympathetic chain, the rate of the denervated heart did not decrease.

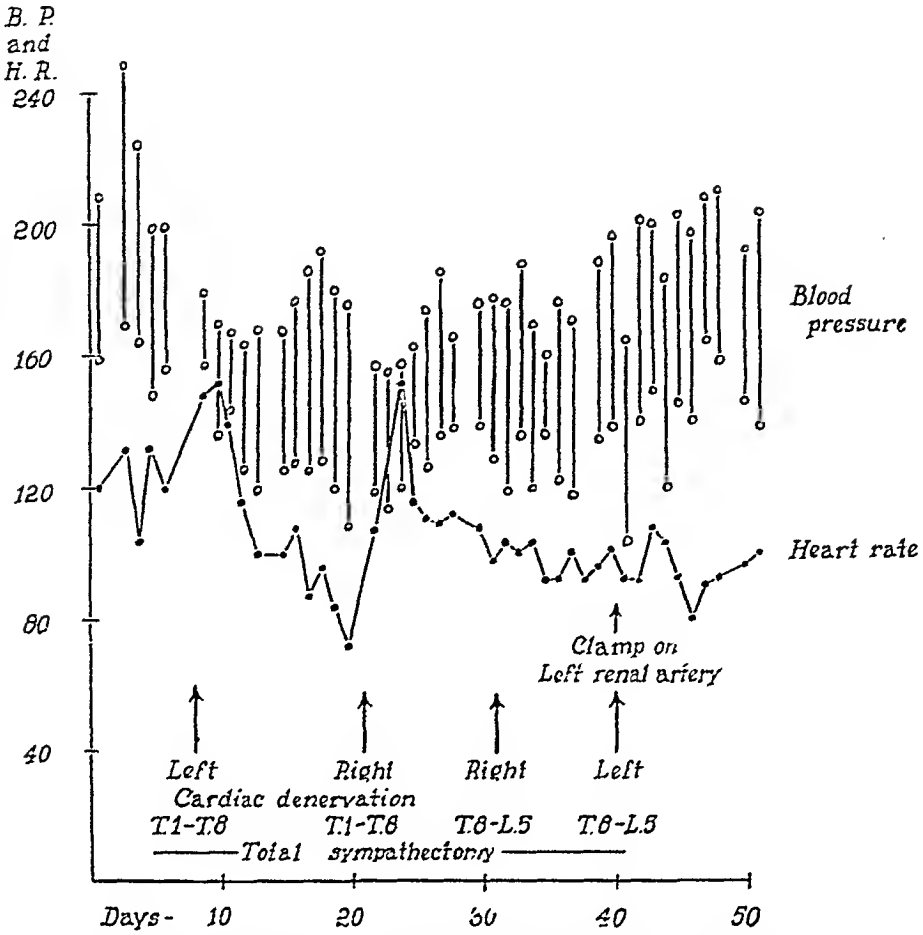


Fig. 4.—Effect of atropine sulfate on heart rate and blood pressure of sympathectomized dog.

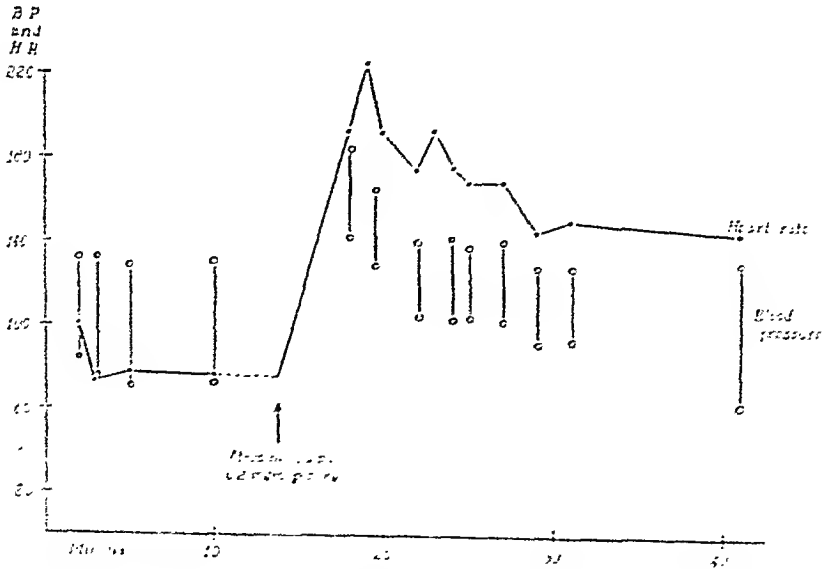


Fig. 5.—Effect of atropine sulfate on heart rate of sympathectomized dog with denervated heart.

This stability of heart rate, indicated that there probably was not an increased medulliadrenal secretion during the course of hypertension produced by compression of the renal artery.

C. *Blood Volume*.—The third physiological mechanism to be investigated as a possible source of elevation of blood pressure, was the plasma

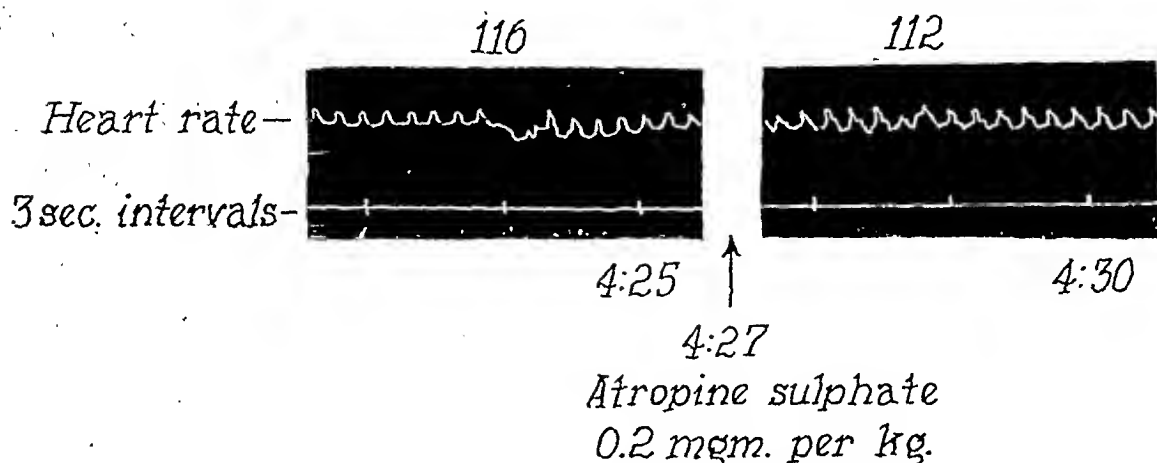


Fig. 6.—Effect of cardiac denervation and total sympathectomy on heart rate of dog with hypertension produced by compression of renal arteries. Right renal artery clamped two weeks before experiment started.

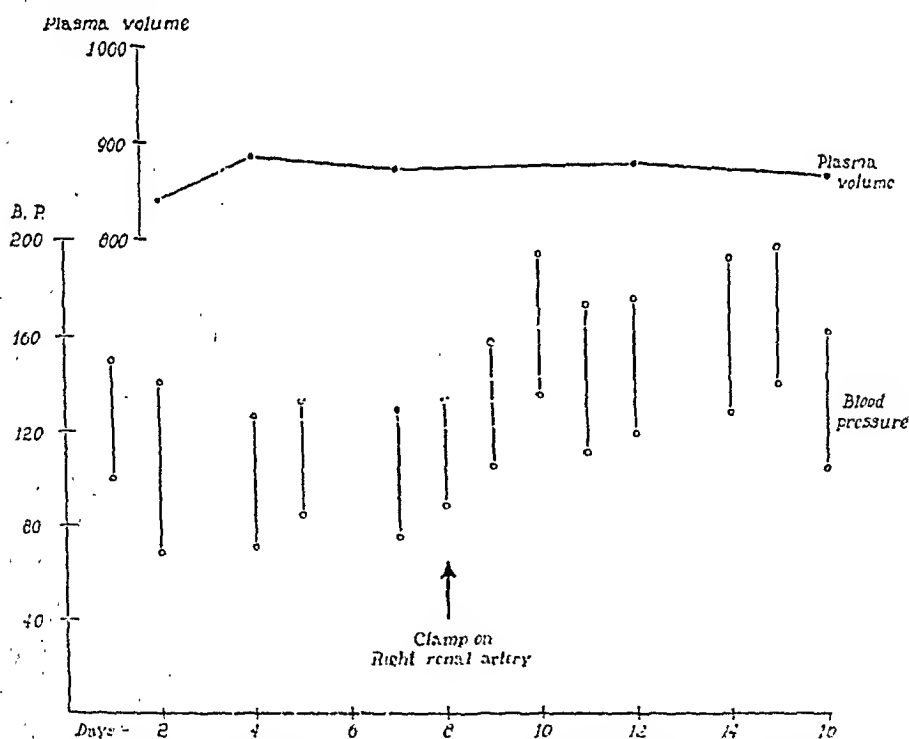


Fig. 7.—Effect of hypertension produced by constriction of renal artery on blood pressure and plasma volume of sympathectomized dog.

volume. It was determined on one normal and two sympathectomized dogs before and after the production of hypertension. As can be seen from Fig. 7, there was no demonstrable increase in the plasma volume as the dog developed hypertension. This result was confirmed in the normal and second sympathectomized dog.

## COMMENT

The production of hypertension by compression of the renal arteries in the completely sympathectomized dog (Figs. 1, 2, 6 and 7) is in accord with the observations of other investigators<sup>1, 2, 3, 5, 21</sup> who studied the effects of partial sympathectomy on this type of hypertension. The completeness of the operative procedures in these experiments was confirmed by inspection of the sympathetic chains (Figs. 1 and 3). Post-mortem dissection of three sympathectomized dogs, which died several days after the production of hypertension, failed to disclose overlooked ganglia or regenerated sympathetic fibers.

Resection of both thoracolumbar chains, although it disconnects the blood vessels from reflex control of the sympathetic nervous system, does not remove all the sympathetic ganglia. There are ganglia located in the periphery, such as the superior cervical, celiac, superior and inferior mesenteric ganglia, which may be of significance. Evidence has recently been brought forward by Govaerts,<sup>14</sup> that a discharge of impulses takes place from the stellate ganglion, even though the pre-ganglionic sympathetic fibers coming to it from the spinal cord have been divided. These observations have not yet been confirmed. Even though these outlying sympathetic ganglia are found to be physiologically active, it is unlikely that they are of significance in the development or maintenance of hypertension since their connections with the central nervous system have been severed. There is still the possibility, however, that they might be activated through stimulating agents carried by the blood stream.

The blood pressure of normal dogs drops for some days after removal of both sympathetic chains.<sup>7, 15</sup> In one of our animals with spontaneous hypertension (Fig. 2) a similar fall is illustrated. The hypertension produced by denervation of the carotid sinuses and section of the depressor nerves, also disappears after total sympathectomy.<sup>16</sup> Yet in the dogs in which hypertension was produced by compression of the renal arteries, the blood pressure was not reduced to normal, even immediately after operation (see Figs. 3 and 6). In "carotid sinus" hypertension, an increase in adrenal secretion has been noted.<sup>17</sup> In our experiments, there was no evidence of an increase in activity of the adrenal medulla (Fig. 6). From these observations, it would seem unlikely that the hypertension from compression of the renal arteries was the result of increased activity of the sympathetic nervous system or the adrenal medulla.

The completely sympathectomized dog is able to engage in vigorous physical work with only slight impairment of efficiency.<sup>18</sup> The increased cardiac activity produced through the cardio-accelerator fibers of the vagus nerves, probably assists in maintaining an adequate head of pressure in the arterial system. In order to eliminate reflex cardiac

control as a mechanism for the production of "renal" hypertension, it was necessary to denervate the heart by intrathoracic section of all cardiac nerves. Even denervation of the heart, combined with total sympathectomy (Fig. 6), did not prevent the development of hypertension.

Determinations of the plasma volume in experimental "renal" hypertension have not been reported. In clinical cases of nephritis<sup>19</sup> and hypertension<sup>20</sup> no consistent increase has been observed. The unchanged plasma volume in hypertensive dogs, found in these experiments, is in agreement with the observations in clinical cases.

#### SUMMARY

1. Complete sympathectomy, in seven dogs, did not prevent the development of hypertension from compression of the renal arteries.
2. The level of the hypertension was not materially affected during the course of total sympathectomy.
3. There was no evidence of increased medulliadrenal secretion.
4. Injection of ergotamine tartrate (3 mg.) produced a slight further increase in the hypertension in two dogs but this dose was insufficient to reverse the pressor effect of adrenalin (0.3 c.c. 1:1000 intravenously).
5. Denervation of the heart, combined with total sympathectomy, did not influence the course of the hypertension.
6. The plasma volume, in one normal and in two sympathectomized dogs, was not increased as the hypertension developed.

#### CONCLUSIONS

Hypertension produced by compression of the renal arteries is not mediated through increased peripheral resistance of reflex sympathetic vasomotor origin.

It is not the result of reflex changes in cardiac activity.

It is not accounted for by an increased volume of plasma.

These observations suggest that the known physiological factors which normally control the level of arterial pressure are not etiologically significant in the genesis of experimental hypertension, produced by compression of the renal arteries.

#### REFERENCES

1. Goldblatt, H., Lynch, J., Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension. I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* 59: 347, 1934.
2. Page, I. H.: The Relationship of the Extrinsic Renal Nerves to the Origin of Experimental Hypertension, *Am. J. Physiol.* 112: 166, 1935.
3. Collins, D. A.: Hypertension From Constriction of the Arteries of Denervated Kidneys, *Am. J. Physiol.* 116: 616, 1936.
4. Wood, J. E., Jr., and Cash, J. R.: Experimental Hypertension—Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs, *J. Clin. Investigation* 15: 543, 1936.

5. Goldblatt, H., Gross, J., and Hanzal, R. F.: Studies on Experimental Hypertension. II. The Effect of Resection of Splanchnic Nerves on Experimental Renal Hypertension, *J. Exper. Med.* 65: 233, 1937.
6. Allen, F. M.: Auscultatory Estimation of the Blood Pressure of Dogs, *J. Metabolic Research* 4: 431, 1923.
7. Cannon, B.: The Effects of Progressive Sympathectomy on Blood Pressure, *Am. J. Physiol.* 97: 592, 1931.
8. Cannon, W. B., Newton, H. F., Bright, E. M., Menkin, V., and Moore, R. M.: Some Aspects of the Physiology of Animals Surviving Complete Exclusion of Sympathetic Nerve Impulses, *Am. J. Physiol.* 89: 84, 1929.
9. Cannon, W. B., Lewis, J. T., and Britton, S. W.: Studies on the Conditions of Activity in Endocrine Glands. XVII. A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion, With Evidence for Accessory Accelerator Fibers From the Thoracic Sympathetic Chain, *Am. J. Physiol.* 77: 326, 1926.
10. White, J. C., Garrey, W. E., and Atkins, J. A.: Cardiac Innervation, *Arch. Surg.* 26: 765, 1933.
11. Gregersen, M. I., Gibson, J. J., and Stead, E. A.: Plasma Volume Determination With Dyes: Errors in Colorimetry; Use of the Blue Dye T-1824, *Am. J. Physiol. (Proc.)* 113: 54, 1935.
12. Dale, H. H.: On Some Physiological Actions of Ergot, *J. Physiol.* 34: 163, 1906.
13. Jourdan, F., and Nowak, S. J. G.: Les Fibres Cardio-accéleratrices dans le Nerf Pneumogastrique du Chien, *Compt. rend. Soc. de biol.* 117: 234, 1934.
14. Govaerts, J.: Contribution à l'étude de l'innervation sympathique du cœur, *Arch. internat. de méd. expér.* 11: 630, 1936.
15. Wilson, H., Roome, N. W., and Grimson, K.: Complete Sympathectomy. Observations of Certain Vascular Reactions During and After Complete Exclusion of the Sympathetic Nervous System in Dogs, *Ann. Surg.* 103: 498, 1936.
16. Heymans, C., and Bouchaert, J. J.: Hypertension Artérielle Experimentale et Sympathectomie, *Compt. rend. Soc. de biol.* 120: 82, 1935.
17. Heymans, C.: Le Sinus Carotidien, G. Doin et Cie, Paris, 106, 1933.
18. Brouha, L., Cannon, W. B., and Dill, D. B.: The Heart Rate of the Sympathectomized Dog in Rest and Exercise, *J. Physiol.* 87: 345, 1936.
19. Linder, G. C., Lundsgaard, C., Van Slyke, D. D., and Stillman, E.: Changes in the Volume of Plasma and Absolute Amount of Plasma Proteins in Nephritis, *J. Exper. Med.* 39: 921, 1924.
20. Schmidt, W.: Blutnengen-Bestimmungen bei Nieren und Herzkrankheiten, *Ztschr. f. d. ges. exper. Med.* 58: 276, 1927.
21. Page, I. H.: Unpublished observation.

## THE PHYSIOLOGICAL EFFECTS OF EXTENSIVE SYMPATHECTOMY FOR ESSENTIAL HYPERTENSION\*

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ROCHESTER, MINN.

THIS study of physiological changes resulting from extensive sympathectomy is based on forty-five patients who were operated on for essential hypertension from February, 1935 to January, 1937. Studies of patients operated on since January, 1937 are not included in this report. The technique used, which has been described in detail elsewhere,<sup>1, 3</sup> consists of bilateral subdiaphragmatic, extraperitoneal resection of the splanchnic nerves, celiac ganglions, and the upper two lumbar sympathetic ganglions. The second operation is performed about ten days after that on the opposite side. In twenty-five instances partial suprarenalectomy was performed; one-third to two-fifths of each gland was removed to see if this would accentuate the effects on blood pressure of extensive sympathectomy. Surgical treatment of hypertension has been attempted because it is apparent that there is no means of controlling hypertension adequately, by nonsurgical management, in many instances; the high mortality from hypertension is adequate testimony for this observation.<sup>1, 2</sup>

It is known that elevation of blood pressure in essential hypertension is due to a generalized increase in resistance to the flow of blood through the periphery of the arterial system. The fault, which seems to be that of the arterioles chiefly, appears to be abnormal vasoconstriction or increased arteriolar tonus, at least in early stages of hypertension. Later in the disease organic changes affecting small arteries and arterioles may contribute to increased resistance to the flow of blood through them. There is evidence that, at least in early hypertension, the abnormal state of the arterioles is an expression of abnormal vasomotor stimuli arising in the vasomotor center, which are transmitted to arterioles by way of sympathetic nerves, or that the arterioles respond with an abnormal state of vasoconstriction or tonus to normal stimuli transmitted by way of the sympathetic nervous system. In advanced hypertension the arterioles may assume an independent function of increased resistance to the flow of blood through them either by virtue of structural changes or by virtue of an inherently increased tonus independent of stimuli transmitted over the sympathetic nervous system from the vasomotor center. Goldblatt's experimental work<sup>7</sup> has shown that diminution of blood supply to the kidneys produces hypertension closely simulating essential hy-

\*From the Division of Medicine and the Section on Neurological Surgery, The Mayo Clinic.

Read before the American Heart Association, Section for the Study of the Peripheral Circulation, at Atlantic City, N. J., June 7, 1937.



pertension of man. Whether or not this mechanism of elevation of blood pressure is effective in essential hypertension of man cannot, at present, be either categorically affirmed or denied but the possibility of it must be considered.

The chief purposes of sympathectomy are disconnection of the arterioles from the vasomotor center, thus inducing a state of decreased tonus or of decreased vasoconstriction, and of increasing blood flow through the kidneys by performing sympathetic denervation of them. The reduction of blood pressure by operation may depend on either or both of these effects which may decrease the resistance offered by arterioles to flow of blood through them. Previous experience with cervicothoracic and lumbar sympathectomy indicated that these procedures were of little avail in the treatment of essential hypertension. The failure of these procedures seemed based largely on the probable fact that too small a part of the arteriolar bed was sympathectomized or that sympathetic denervation of the kidneys was not accomplished. The next logical step was splanchnic and upper lumbar sympathectomy, for within the abdomen there exists a relatively enormous arteriolar bed. Diminished liberation of epinephrine from the suprarenal glands may occur incidental to operation and may perhaps contribute importantly to reduction of blood pressure. Also extensive sympathectomy for hypertension may decrease a state of increased tonus in the arterioles of the kidneys, thus improving circulation to them and reducing blood pressure.

Experience has taught us that the surgical procedure employed does not produce uniform effects on blood pressure. We recognize that return of the blood pressure to normal is desirable in essential hypertension but that this does not occur routinely as a result of operation. However, we believe that while such an accomplishment is desirable it is not necessary, for substantial reduction of the blood pressure may relieve symptoms, prevent the disastrous results of sustained abnormally high blood pressure, and prevent marked increases in blood pressure resulting from emotional stimuli which are themselves harmful. We do not believe that surgical operation for hypertension is necessarily the ultimate contribution to the treatment of this serious condition but the results which we have observed following operation have encouraged us to continue with this type of treatment until a better method has been devised.

#### SELECTION OF PATIENTS WITH ESSENTIAL HYPERTENSION FOR EXTENSIVE SYMPATHECTOMY

Some patients with essential hypertension do not require operation for the elevation of blood pressure is not great, does not gradually increase, and does not produce significant changes in the arterial system. Perhaps, as more information is gathered relative to the effects of operation, more patients who have mild, apparently nonprogressive

hypertension will be operated on as a prophylactic measure. However at present we reserve operation, largely, for patients whose hypertension, if mild, is definitely progressive in spite of medical supervision and for those who have severe hypertension which has not responded to medical treatment. Following extensive sympathectomy the blood pressure is not decreased in the same degree in all cases of essential hypertension in which permanent reduction of blood pressure is an urgent need. If patients of this classification who have this disease are operated on, the results vary from extremely good to very poor. This has led us to attempt to select, from a large group of patients who have essential hypertension, those whose blood pressures will respond favorably to operation. We know no infallible criteria for such a selection at the present time. However, patients whose blood pressures decrease to normal or nearly to normal as results of rest or sleep, of oral administration of 3 grains (0.2 gm.) of sodium amytal hourly for three successive hours, of administration of one-half grain of sodium nitrite at half-hour intervals for three hours, and of the slow, intermittent, intravenous injection of a 5 per cent solution of pentothal sodium for light anesthetization, receive the greatest benefit from operation.<sup>4\*</sup> Good results from these tests indicate to us that the arterioles offer increased resistance to flow of blood through them largely by virtue of functional, hence reversible changes; not as a result of organic, hence largely irreversible changes. Conversely, those patients whose blood pressures do not decrease satisfactorily as a result of these measures, benefit from operation, as a group, to a substantially less degree than do those whose pressures are still labile.

Unfortunately for extreme accuracy of prediction of results of operation, an occasional but infrequent patient whose blood pressure does not decrease satisfactorily as a result of rest, of administration of amytal, of sodium nitrite, or of pentothal, receives benefit from operation while not infrequently a patient for whom prediction of excellent operative effects on blood pressure, based on satisfactory responses to the tests mentioned before operation, receives much less than the expected benefit from operation. In Table I it is shown that when the response of the blood pressure to intravenous injection of pentothal is unfavorable the results of operation are almost uniformly unfavorable and that when the response of the blood pressure to the intravenous injection of pentothal sodium is fairly good, the eventual result is fairly good. However, when the responses of the blood pressure to the intravenous injection of pentothal sodium are good, the eventual effects of operation on the blood pressure are occasionally much less satisfactory. Since the greatest errors in predicting results occur when good results of operation are anticipated and since the tendency is to predict too good results on the basis of preoperative tests, we believe

\*Incomplete studies indicate that pressure on carotid sinuses may affect blood pressure to much the same degree that rest, amytal, sodium nitrite, and pentothal affect it.

TABLE I

EFFECTS ON BLOOD PRESSURE OF PENTOTHAL AND EXTENSIVE SYMPATHECTOMY

| RESPONSE OF BLOOD PRESSURE |                   | RESULT OF OPERATION |        | ACCURACY OF PREDICTION |
|----------------------------|-------------------|---------------------|--------|------------------------|
| TO PENTOTHAL               | TO OPERATION*     | PREDICTION          | ACTUAL |                        |
| 158/132                    | Dead in seven mo. | Poor                | Poor   | Good                   |
| 170/130                    | 160/120 (9)†      | Poor                | Poor   | Good                   |
| 165/122                    | 155/110 (11)      | Poor                | Poor   | Good                   |
| 184/134                    | 255/160 (9)       | Poor                | Poor   | Good                   |
| 146/106                    | 168/100 (9)       | Fair                | Fair   | Good                   |
| 150/112                    | 154/106 (8)       | Fair                | Fair   | Good                   |
| 158/112                    | 190/120 (7)       | Fair                | Poor   | Poor                   |
| 154/110                    | 194/120 (9)       | Fair                | Poor   | Poor                   |
| 148/114                    | 200/130 (6)       | Fair                | Poor   | Poor                   |
| 154/116                    | 170/115 (2)       | Fair                | Fair   | Good                   |
| 132/106                    | 174/118 (10)      | Fair                | Fair   | Poor                   |
| 158/ 98                    | 194/120 (6)       | Fair                | Poor   | Poor                   |
| 120/ 90                    | 140/100 (5)       | Good                | Good   | Good                   |
| 142/100                    | 150/ 90 (4)       | Good                | Good   | Good                   |
| 118/ 90                    | 170/100 (10)      | Good                | Fair   | Fair                   |
| 140/100                    | 180/110 (5)       | Good                | Fair   | Fair                   |

\*Mean of three determinations.

†Months after operation.

it advisable to accept the least favorable response of the blood pressure to rest and sleep, and to administration of amytal, sodium nitrite, and pentothal as the basis of preoperative prediction. We do not consider apparent sclerosis of the retinal arteries, moderate enlargement of the heart, inversion of T-waves in electrocardiograms, albuminuria, slight reduction in renal function or cerebrovascular accident from which recovery has been satisfactory, contraindications, in themselves, to operation. However, we do not advise operation for patients who have congestive heart failure, marked renal insufficiency, advanced arteriosclerosis, or angina pectoris. Perhaps as experience increases some of these patients may be considered suitable subjects for operation.

## MORTALITY AND MORBIDITY

A series of eighty-five successive operations has been performed without a death. Three patients have died subsequently. A girl, seven years of age, with hypertension of Group IV (malignant hypertension)<sup>1, 2\*</sup> and repeated convulsions died seven months following operation which did not influence the blood pressure significantly. A man, aged forty-one years, with renal and myocardial failure owing to hypertension of Group II died seven months after operation which did not significantly influence blood pressure. A woman, twenty-five years old, with hypertension of Group III which was fixed sufficiently that the minimal blood pressures during rest and sleep were 160 and 120 died fourteen months following operation. Because of information we have gained we would consider none of these patients suitable candidates for operation at the present time. A patient whose blood pressure was very favorably influenced by operation and whose physical condition was good committed suicide because of depression resulting from business

\*The classification of essential hypertension is that of Keith and Wagener.

worries. Two patients have had cerebral hemorrhages. The remainder of the entire group of patients are not disabled although the blood pressure of many of them was not greatly decreased by operation, as will be emphasized later. The symptoms of many patients of this group were not benefited by operation.

EFFECT OF OPERATION ON BLOOD PRESSURE AND PULSE RATE  
WHEN PATIENTS STAND

It is a common observation that after operation the blood pressure decreases and the pulse rate increases when the patient stands. While such reactions are common to some degree in many instances before operation, they are usually greatly exaggerated after operation (Table II). These disturbances undoubtedly account, at least in a major de-

TABLE II

EFFECT OF UPRIGHT POSTURE ON PULSE RATE AND BLOOD PRESSURE FOLLOWING  
OPERATION\*

(TEN ILLUSTRATIVE CASES)

| BLOOD PRESSURE   |          |                 |          | PULSE RATE       |          |                 |          |
|------------------|----------|-----------------|----------|------------------|----------|-----------------|----------|
| BEFORE OPERATION |          | AFTER OPERATION |          | BEFORE OPERATION |          | AFTER OPERATION |          |
| LYING            | STANDING | LYING           | STANDING | LYING            | STANDING | LYING           | STANDING |
| 220/110          | 200/110  | 170/95          | 80/50    | 112              | 104      | 84              | 120      |
| 198/116          | 200/126  | 160/106         | 140/102  | 94               | 108      | 80              | 124      |
| 154/110          | 148/112  | 134/94          | 128/90   | 80               | 116      | 76              | 120      |
| 150/108          | 160/114  | 128/92          | 110/92   | 72               | 124      | 88              | 115      |
| 168/114          | 182/130  | 158/110         | 118/92   | 88               | 120      | 120             | 156      |
| 182/116          | 164/120  | 140/112         | 118/92   | 80               | 92       | 92              | 124      |
| 200/110          | 192/120  | 192/110         | 148/116  | 84               | 100      | 92              | 138      |
| 162/110          | 162/122  | 194/122         | 94/78    | 84               | 108      | 88              | 120      |
| 210/138          | 208/146  | 178/118         | 70/40    |                  |          | 100             | 138      |
| 200/130          | 165/120  | 136/100         | 114/80   |                  |          | 84              | 121      |

\*Two to three weeks following operation.

gree, for weakness (and occasionally syncope), breathlessness, and palpitation which are commonly noted by patients when they stand following operation.

Usually orthostatic tachycardia and hypotension disappear gradually over variable periods following operation (Table III). This occurs independently of whether the effect of operation on the blood pressure was good, for in cases of poor and good results alike there is a gradual tendency of response of the pulse rate and blood pressure to the upright position to be less marked as time passes after operation. Frequently orthostatic tachycardia persists after orthostatic hypotension has disappeared.

EFFECT OF OPERATION ON THE RESPONSE OF THE BLOOD PRESSURE  
TO IMMERSION OF A HAND IN COLD WATER

We place a good deal of importance on the response of the blood pressure to a standard stimulus, for which we use the cold test devised by Hines and Brown.<sup>8</sup> This test is carried out by determining blood

TABLE III

THE EFFECT OF THE UPRIGHT POSTURE ON BLOOD PRESSURE; VARYING PERIODS  
AFTER OPERATION  
(TEN ILLUSTRATIVE CASES)

| TIME AFTER OPERATION | BLOOD PRESSURE |          |
|----------------------|----------------|----------|
|                      | LYING          | STANDING |
| Two weeks            | 170/120        | 160/115  |
| Sixteen months       | 188/120        | 200/130  |
| Two weeks            | 120/90         | 80/60    |
| Four months          | 140/95         | 135/95   |
| Two weeks            | 164/112        | 138/120  |
| Ten months           | 214/130        | 234/140  |
| Two weeks            | 194/122        | 94/78    |
| Three months         | 230/125        | 255/160  |
| Two weeks            | 168/112        | 132/100  |
| Six months           | 160/140        | 152/130  |
| Two weeks            | 170/95         | 80/50    |
| Two months           | 210/126        | 192/120  |
| Two weeks            | 148/104        | 134/110  |
| Ten months           | 165/122        | 185/135  |
| Two weeks            | 110/86         | 80/65    |
| Ten months           | 108/88         | 134/98   |
| Two weeks            | 134/96         | 122/90   |
| Eight months         | 118/94         | 120/96   |
| Two weeks            | 118/88         | 68/58    |
| Four months          | 110/80         | 115/100  |

pressure with the patient resting, until it reaches a basal level. A hand is then immersed to the wrist in water at 4° C. for one minute and blood pressure determined at the end respectively of thirty seconds and of one minute of immersion of the hand. The highest value is considered characteristic of the response. We believe that the response of the blood pressure to this test is a measure of the way in which it responds on innumerable occasions to such stimuli as anxiety, fright, and mental stresses and strains. In Table IV it is shown that when the blood pressure has been favorably influenced by operation, the increase in it as a result of the cold test is greatly reduced in most instances. This is particularly true of the systolic blood pressure. When operation does not produce a significant decrease in the blood pressure, the response of it to the cold test is ordinarily less than before operation but distinctly abnormal (Table V). As in cases in which operation has produced significant decrease in blood pressure, the systolic blood pressure responds less sharply to the test than does the diastolic pressure.

#### EFFECT OF OPERATION ON SYMPTOMS RESULTING FROM HYPERTENSION

The effect of operation on symptoms, while variable, is roughly proportional to the effect on blood pressure. However, not infrequently patients note relief of headache, fatigue, pain in the chest, "dizziness," and nervousness in spite of the fact that the blood pressure has not

TABLE IV

RESPONSE OF THE BLOOD PRESSURE TO THE COLD TEST IN CASES IN WHICH THE EFFECT OF OPERATION ON THE BLOOD PRESSURE WAS FAVORABLE  
(FIFTEEN ILLUSTRATIVE CASES)

| BEFORE OPERATION   | AFTER OPERATION    |
|--------------------|--------------------|
| 168/118 to 192/132 | 128/100 to 138/104 |
| 200/110 to 250/130 | 170/95 to 210/120  |
| 190/135 to 260/170 | 128/100 to 154/122 |
| 190/110 to 238/130 | 136/80 to 170/108  |
| 158/118 to 184/120 | 130/90 to 164/100  |
| 198/116 to 278/160 | 160/106 to 198/130 |
| 200/130 to 240/150 | 136/100 to 140/104 |
| 154/110 to 178/126 | 134/94 to 144/118  |
| 146/100 to 204/135 | 132/90 to 158/118  |
| 170/110 to 200/145 | 130/100 to 175/130 |
| 200/130 to 258/162 | 140/100 to 160/100 |
| 182/102 to 248/150 | 140/90 to 188/128  |
| 158/128 to 190/150 | 126/94 to 150/128  |
| 174/110 to 218/156 | 112/86 to 146/124  |
| 170/118 to 202/134 | 150/106 to 170/120 |

TABLE V

RESPONSE OF THE BLOOD PRESSURE TO THE COLD TEST IN CASES IN WHICH THE EFFECT OF OPERATION ON BLOOD PRESSURE WAS NOT FAVORABLE  
(FIFTEEN ILLUSTRATIVE CASES)

| BEFORE OPERATION   | AFTER OPERATION    |
|--------------------|--------------------|
| 170/130 to 240/156 | 160/122 to 190/136 |
| 156/122 to 190/120 | 152/118 to 185/128 |
| 190/120 to 220/130 | 170/120 to 185/130 |
| 180/120 to 214/144 | 198/132 to 214/136 |
| 200/130 to 240/158 | 200/140 to 220/170 |
| 170/120 to 256/150 | 166/114 to 200/150 |
| 182/116 to 230/150 | 140/112 to 178/128 |
| 210/134 to 232/176 | 200/119 to 210/128 |
| 192/120 to 238/146 | 190/122 to 236/150 |
| 180/112 to 240/140 | 170/112 to 174/120 |
| 192/120 to 230/165 | 195/135 to 225/160 |
| 170/120 to 235/160 | 175/120 to 210/140 |
| 190/120 to 240/175 | 170/120 to 218/136 |
| 200/136 to 250/146 | 170/112 to 204/138 |
| 170/118 to 236/160 | 180/120 to 218/156 |

been greatly reduced by operation. It is probable that some of the symptoms associated with hypertension, such as headache, may occur only when the pressure reaches an excessively high level. Operation which may reduce blood pressure only slightly may lower it enough so that some of the symptoms do not occur. There seems no other logical explanation for the observation that relief of symptoms is much more marked than reduction of blood pressure in many instances. In most instances in which the blood pressure has been greatly reduced by operation headache is relieved, pain in the chest disappears, fatigue is lessened, and the patients gain weight and feel in general greatly improved. Many of them note diminution of nervousness and of a "let down" feeling, which gratifies them. Some patients have stated they feel "entirely well" or "better than in several years." In general, about 70 per cent of the entire group of patients were benefited

clinically. Some patients whose blood pressure has been greatly reduced by operation continue to note undue fatigue, weakness, and dyspnea for weeks or months after operation. One patient whose condition was followed closely did not regain normal strength until about six months after operation. We have not been able to determine definitely that the patients who notice these symptoms following operation are those who continue to have orthostatic hypotension but it appears that this is so.

*Effect of Operation on Sweating.*—The area of anhidrosis following operation is variable and not always equal in extent on the right and left sides. Extensiveness of anhidrosis depends on what part of the thoracolumbar sympathetic chain is resected at the time of operation. In the various cases studied the greatest area of anhidrosis begins at a line midway between the umbilicus and symphysis and extends distally.

*Effect of Operation on the Heart.*—When operation is successful, T-waves originally inverted in the electrocardiogram may become upright and the transverse diameter of the heart demonstrated by roentgen films exposed at 6 feet may decrease. Tachycardia occurs commonly when the patient stands after operation. When orthostatic hypotension is marked following operation, the increase in the pulse rate when the patient stands is also marked; 120 beats per minute is commonly observed and occasionally the cardiac rate is as great as 150 beats per minute when the patient stands. As time passes after operation, the increase in the rate of the heart when the patient stands decreases and the improvement parallels roughly decrease in orthostatic hypotension. However, tachycardia when the patient stands may persist after orthostatic hypotension disappears.

*Effect on Renal Function.*—Most of our patients who were operated on had no significant impairment of renal function; patients whose renal function was impaired were not operated on. Since we have not had opportunity to study the renal function of many of our patients after considerable time following operation has elapsed, and since tests for renal function when function is not significantly impaired are not always reliable for comparative purposes, we cannot say that renal function is improved following successful operation. Such an observation has been made by Freyberg and Peet.<sup>6</sup> It is quite apparent that renal function is not impaired when the blood pressure is greatly reduced by operation. This observation agrees with those of Freyberg and Peet,<sup>6</sup> of Page,<sup>9</sup> and of Page and Heuer.<sup>10</sup> Diminution in the amount of albumin in the urine or disappearance of it occurs commonly following successful operation.

*Effect on Temperature and Motor Function of the Extremities.*—Following operation the feet are warm and dry. If the blood pressure has been significantly decreased by operation the hands may be cold, apparently owing to persistence of vasoconstriction in these parts. An

occasional patient notes generally increased tolerance to warmth. The sensation and motor function of the lower extremities are not impaired. An occasional patient mentions an area of numbness, which is variable in extent in different cases and which is due to section of or traction on the lateral branches of the eleventh and twelfth intercostal nerves at the time of operation.

*Effect of Operation on the Retinas.*—The retinas of all our patients were examined by Dr. Wagener, an experienced ophthalmologist. The changes immediately following operation are not constant and cannot be correlated with the effect of operation on the blood pressure. The retinas of patients who are examined several months after operation, and whose blood pressures have not been significantly influenced, have not appreciably changed in appearance in most instances. In instances in which the blood pressure has been greatly reduced by operation, retinitis may disappear, and apparent sclerosis and arterial spasm may be greatly diminished. The cause of this is not entirely clear for reduction of pressure by extensive sympathectomy should not influence spasm of the retinal arteries as sympathetic control of them is not impaired, unless hypertension itself provokes arteriolar spasm or unless operation removes some mechanism which causes both. Again, if the results of the experimental work of Goldblatt<sup>7</sup> can be transferred to human beings with hypertension, it is possible that an increase of the renal blood flow may cause generalized decrease in arterial tonus, thus relieving spasm of the retinal arteries. It is also possible that retinal arterial spasm is compensatory, to prevent rupture in hypertension, and disappears when blood pressure is reduced. However, in spite of a significant reduction in blood pressure, examination of the retinas may disclose changes of the same degree as those observed preoperatively. These observations are in agreement with those of Frailek and Peet.<sup>5</sup>

*Effect of Operation on the Intestines.*—Disturbances of intestinal function were noted in a number of instances in which periods of three to four bowel movements daily, with stools of soft consistency, alternated with periods of normal bowel movements. In some instances constipation was relieved. Flatulence or other evidence of disturbed motor activity of the gastrointestinal tract were uniformly absent.

*Effect of Operation on Sexual Function.*—Ordinarily libido and erection are not impaired. However, some patients note diminished libido. Nocturnal orgasms occur as before operation but emission is usually absent or greatly diminished. Orgasm occurs normally during sexual intercourse but there is either no ejaculation of fluid or the amount is reduced. Male patients may be sterile after operation but this is not certain. Sexual satisfaction may be unimpaired or reduced. Menstruation occurs normally following operation and dysmenorrhea when present before operation may disappear following operation.



*Effect of Operation on Basal Metabolism.*—We have known for a long time that the basal metabolism is increased in many cases of essential hypertension. There is an almost uniform tendency for basal metabolism to be lower two to three weeks following the second operation than it was before operation. However, it is probable that several factors, such as prolonged rest in bed, anesthesia, operation and weakness contribute to reduction of the basal metabolism in addition to the diminution of blood pressure. In Table VI it is shown that of six

TABLE VI  
EFFECT OF OPERATION ON BLOOD PRESSURE AND BASAL METABOLISM  
(EIGHT ILLUSTRATIVE CASES)

| BEFORE OPERATION |                                | AFTER OPERATION* |                                |
|------------------|--------------------------------|------------------|--------------------------------|
| BLOOD PRESSURE   | BASAL METABOLIC RATE, PER CENT | BLOOD PRESSURE   | BASAL METABOLIC RATE, PER CENT |
| 160/100          | +14                            | 140/90           | + 7                            |
| 200/118          | - 9                            | 130/90           | - 4                            |
| 180/120          | + 1                            | 112/80           | -16                            |
| 180/120          | + 9                            | 140/100          | + 7                            |
| 154/90           | +12                            | 116/72           | +18                            |
| 186/112          | - 2                            | 130/80           | .11                            |
| 150/110          | + 3                            | 140/110          | - 2                            |
| 188/120          | +11                            | 160/120          | - 5                            |

\*Two to three weeks.

instances in which there was substantial reduction of blood pressure following operation, in five there was reduction of basal metabolism. However, in two instances in which there was no substantial reduction of blood pressure by operation, the basal metabolism was decreased after operation. We hope to have further information on this interesting subject when we have had opportunity to determine basal metabolism considerable periods of time following operation.

*Effect of Operation on Suprarenal Glands.*—Although partial suprarenalectomy was a part of the surgical procedure in twenty-five instances, Addison's disease has never been observed. No significant changes in the amounts of sodium and chlorides in the blood, as results of operation, have been determined regardless of whether or not the suprarenal glands were partially resected. However, a regular increase in the amount of potassium, averaging 3 mg. in each, has been observed in eight cases, in five of which partial suprarenalectomy was not performed.

#### EFFECTS OF OPERATION ON BLOOD PRESSURE

As stated previously the results of operation for hypertension are not uniform; they vary from extremely poor to excellent. The results depend on selection of patients. At first patients were operated on who would not now be considered suitable for operation. The additional knowledge that operation for hypertension can be carried out with very little risk is further reason for surgical treatment of hypertension.

Whatever may be said about this procedure, it seems undeniably true that the patient is not harmed by it. The impression that some physicians have that operation itself leaves patients disabled and unable to carry on normal activities has no foundation in fact.

An analysis of the results of operation on this group of patients indicates that about 45 per cent of the patients operated on had no material change in blood pressure following operation (Table VII);

TABLE VII  
EFFECT OF OPERATION ON BLOOD PRESSURE  
(TWENTY INSTANCES OF POOR RESULTS)

| BLOOD PRESSURE   |          |         |                 |        |
|------------------|----------|---------|-----------------|--------|
| BEFORE OPERATION |          |         | AFTER OPERATION |        |
| MAXIMUM          | MINIMUM* | MEAN    | PRESSURES†      | MONTHS |
| 205/130          | 160/110  | 180/125 | 192/122         | 19     |
| 210/130          | 150/105  |         | 210/130         | 14     |
| 190/140          | 130/100  | 180/130 | 235/180         | 18     |
| 215/150          | 170/115  | 180/130 | 215/150         | 16     |
| 220/140          | 140/105  | 180/120 | 170/124         | 17     |
| 220/155          | 180/115  | 200/120 | 190/120         | 16     |
| 250/180          | 160/120  | 220/150 | 220/135         | 10     |
| 208/160          | 160/90   |         | 215/150         | 14     |
| 220/140          | 140/100  | 180/110 | 170/130         | 9      |
| 230/160          | 180/112  | 200/130 | 180/130         | 9      |
| 210/150          | 160/110  | 180/130 | 190/130         | 7      |
| 230/140          | 190/115  | 200/126 | 200/130         | 6      |
| 250/140          | 190/100  | 170/100 | 200/120         | 7      |
| 240/160          | 210/110  | 220/130 | 220/170         | 8      |
| 140/190          | 208/170  |         | Dead            | 7      |
| 210/135          | 150/90   |         | 200/125         | 6      |
| 230/154          | 180/130  | 200/134 | 190/130         | 6      |
| 220/130          | 170/120  | 195/125 | 214/130         | 4      |
| 175/120          | 140/95   | 164/112 | 180/120         | 10     |
| 252/145          | 200/110  | 220/115 | 252/134         | 6      |

\*In this table and in Tables VIII and IX the term "minimum" applies to the lowest of twenty-four blood pressures determined hourly and consecutively while the patient rested in bed or slept.

†Rough mean in three determinations.

about 30 per cent received fair results in relation to blood pressure from operation and about 25 per cent received good results (Tables VIII and IX). With the methods of selection which we use now the incidence of failures is materially reduced. In Tables VII, VIII, and IX, it is shown that the minimal blood pressure resulting from rest and sleep before operation is a fairly good indication of the effects of operation on the blood pressure. It is well to emphasize again that errors in prediction of effects of operation on blood pressure are rarely made when preoperative tests indicate a poor result, but that errors of prediction occur occasionally when preoperative tests indicate a good result of operation. As a result of these observations we feel justified ordinarily in refusing to operate on patients when preoperative tests indicate that response of the blood pressure to operation will be unsatisfactory. We do not know that good results which follow operation will persist. Good results which persist for only several

TABLE VIII

EFFECT OF OPERATION ON BLOOD PRESSURE  
(THIRTEEN INSTANCES OF FAIR RESULTS)

| BLOOD PRESSURE   |          |         |                 |        |
|------------------|----------|---------|-----------------|--------|
| BEFORE OPERATION |          |         | AFTER OPERATION |        |
| MAXIMUM          | MINIMUM* | MEAN    | PRESSURES†      | MONTHS |
| 260/160          | 180/120  |         | 160/106         | 17     |
| 235/120          | 175/110  |         | 190/110         | 14     |
| 230/136          | 170/110  | 190/120 | 156/104         | 12     |
| 220/120          | 140/100  | 180/110 | 180/104         | 12     |
| 210/168          | 168/110  | 180/120 | 150/104         | 11     |
| 230/140          | 140/90   | 160/110 | 160/106         | 9      |
| 210/140          | 130/75   |         | 150/108         | 8      |
| 200/120          | 145/90   | 170/105 | 170/?           | 3      |
| 228/142          | 170/108  | 200/120 | 182/110         | 5      |
| 205/130          | 130/90   |         | 170/100         | 5      |
| 200/130          | 140/108  | 160/120 | 170/115         | 3      |
| 260/140          | 200/130  | 235/135 | 170/104         | 2      |
| 210/130          | 170/120  |         | 170/115         | 2      |

\*.†see Table VII.

TABLE IX

EFFECT OF OPERATION ON BLOOD PRESSURE  
(ELEVEN INSTANCES OF GOOD RESULTS)

| BLOOD PRESSURE   |          |         |                 |        |
|------------------|----------|---------|-----------------|--------|
| BEFORE OPERATION |          |         | AFTER OPERATION |        |
| MAXIMUM          | MINIMUM* | MEAN    | PRESSURES†      | MONTHS |
| 205/135          | 140/100  | 160/110 | 150/90          | 23     |
| 225/130          | 150/100  | 190/110 | 128/90          | 15     |
| 240/105          | 130/95   |         | 160/90          | 15     |
| 190/135          | 140/90   | 160/114 | 140/100         | 15     |
| 180/114          | 144/90   | 174/110 | 150/90          | 15     |
| 240/140          | 145/100  | 170/120 | 128/80          | 14     |
| 220/150          | 170/120  | 190/130 | 140/100         | 13     |
| 205/120          | 175/90   | 200/110 | 165/95          | 10     |
| 200/135          | 150/90   | 180/114 | 140/100         | 5      |
| 220/140          | 146/78   | 230/150 | 140/?           | 3      |
| 210/130          | 150/92   | 170/110 | 140/78          | 2      |

\*.†see Table VII.

months may justify operation, for patients are relieved of distressing and frequently disabling symptoms. For example, some patients feel that operations were worth while because of the relief of headache, if for no other reason.

#### CONCLUSIONS

1. The results of operation for essential hypertension can be predicted with reasonable certainty by observing the response of the blood pressure to rest and sleep, to ingestion of sodium amytal and sodium nitrate, and to intravenous injection of pentothal sodium. When poor results of operation are predicted as a result of these tests, the results are almost uniformly unfavorable. When good results are predicted, some patients do not receive as much benefit from operation as was anticipated.

2. There have been no operative deaths in a series of eighty-five cases. The operation itself does not disable, although anhidrosis of the lower extremities and loss of ejaculation and probably of fertility of the male result.

3. Following operation orthostatic hypotension and tachycardia occur but disappear as time passes.

4. Operation diminishes the response of the blood pressure to immersion of a hand in ice water.

5. Operation usually relieves symptoms when blood pressure is greatly reduced but may do so when there results no great reduction of blood pressure. About 70 per cent of patients were benefited clinically.

6. As a result of operation the heart may decrease in size, inverted T-waves in the electrocardiogram may become upright, retinitis and spasm of the retinal arteries may diminish or disappear, albuminuria may decrease, and renal function may be improved. The basal metabolism may be decreased.

7. The blood pressure was not materially reduced by operation in 45 per cent of this series of patients. Many of these patients would not be operated on now because preoperative tests would indicate that operation would not significantly reduce the blood pressure. About 30 per cent received fair results in relation to blood pressure and 25 per cent of them received excellent results.

#### REFERENCES

1. Adson, A. W., and Allen, E. V.: Essential Hypertension: I. General Considerations, *Proc. Staff Meet., Mayo Clin.* 12: 1, 1937. II. The Rationale and Methods of Surgical Treatment, *Ibid.* 12: 49, 1937. III. Selection of Patients for and Results of Surgical Treatment, *Ibid.* 12: 75, 1937.
2. Adson, A. W., and Allen, E. V.: Essential Hypertension: General Considerations and Report of Results of Treatment by Extensive Resection of Sympathetic Nerves and Partial Resection of Both Suprarenal Glands, *Proc. Inter-State Postgrad. Med. Assemb. N. Amer.*, p. 181, 1936.
3. Adson, A. W., Craig, W. McK., and Brown, G. E.: Surgery in Its Relation to Hypertension, *Surg. Gynec. & Obst.* 62: 314, 1936.
4. Allen, E. V., Lundy, J. S., and Adson, A. W.: Preoperative Prediction of Effects on Blood Pressure of Neurosurgical Treatment of Hypertension, *Proc. Staff Meet., Mayo Clin.* 11: 401, 1936.
5. Fralick, F. B., and Peet, M. M.: Hypertensive Fundus Oculi After Resection of the Splanchnic Sympathetic Nerves; a Preliminary Report, *Arch. Ophth.* 15: 840, 1936.
6. Freyberg, R. H., and Peet, M. M.: The Effect on the Kidney of Bilateral Splanchnicectomy in Patients With Hypertension, *J. Clin. Investigation* 16: 49, 1937.
7. Goldblatt, Harry: Experimental Hypertension Due to Renal Ischemia. Read at twenty-first annual session of American College of Physicians, St. Louis, 1937.
8. Hines, E. A., Jr., and Brown, G. E.: Cold Pressor Test for Measuring Reactibility of the Blood Pressure: Data Concerning 571 Normal and Hypertensive Subjects, *AM. HEART J.* 11: 1, 1936.
9. Page, I. H.: The Effect on Renal Efficiency of Lowering Arterial Blood Pressure in Cases of Essential Hypertension and Nephritis, *J. Clin. Investigation* 13: 909, 1934.
10. Page, I. H., and Heuer, G. J.: The Effect of Renal Denervation on the Level of Arterial Blood Pressure and Renal Function in Essential Hypertension, *J. Clin. Investigation* 14: 27, 1935.

## OBSERVATIONS ON PHLEBITIS\*

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MUCH has been said on the subject of thrombosis and phlebitis, yet for the most part the etiology is still obscure and the treatment diversified and unsatisfactory. It is necessary to be skeptical of some of our so-called "fundamentals" until more data are secured. The observations here described are of diverse nature, and are not presented in any effort to arrive at conclusive deductions, but rather in the hope that they will arouse a critical viewpoint and lead to further clarification of our problem.

### THE RÔLE OF INFECTION IN THROMBOPHLEBITIS

It may be of interest to examine the evidence in regard to the rôle of infection in the production of thrombophlebitis. In this respect phlebitis can quite easily be divided into two major groups, suppurative and nonsuppurative.

Suppurative phlebitis is seen in the immediate vicinity of a purulent focus, such as mastoiditis, septic endometritis, or carbuncle. It takes no special argument to establish the presence of infection in this form. The involved vein may not show any more clinical signs of inflammation than a bland phlebitis. The clot within it, however, is infected, and it undergoes purulent softening with a dissemination of bacteria and portions of clot throughout the blood stream. Wherever large enough masses of clot or bacteria block branches of the pulmonary artery, infarcts result, which go on to pulmonary abscess formation. Microscopic examination of the primary (autochthonous) portion of the thrombus shows the vein wall infiltrated with an exudate rich in polymorphonuclear leucocytes (Fig. 1). The bacteria are invariably found in this part of the vein and its contained clot. It may be noted that the *propagated* portion of the clot may be free of bacteria and the vein wall far from the original focus may show an exudate poor in polymorphonuclear leucocytes.

In the nonsuppurative category may be classed most of the cases of postoperative phlebitis, especially when it is not in the vicinity of the operative wound; as well as phlebitis of varicose veins, and finally the so-called "marantic phlebitis" occurring in fevers and in terminal states. At first glance such phlebitis might also seem to be a septic

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This study was aided by a grant from the Charlton Research Fund.

Read before The American Heart Association, section for the study of the peripheral circulation, at Atlantic City, N. J., June 7, 1927.

process. The involved vein is apt to be very hot and tender, and the swelling, augmented by phlebitic edema, may be considerable. Nevertheless the evidence for the presence of bacteria in this group is controversial and stands in considerable contrast to the clear-cut demonstration of bacteria in the septic variety.

The bland nature of nonsuppurative phlebitis had seemed well established by the work of Virchow.<sup>1</sup> With the advent of bacteriological examinations the picture was reversed. Vaquez,<sup>2</sup> in 1890, recorded the finding of micrococci in what had previously been called marantic thrombi, in patients dying of typhoid fever, tuberculosis, and even cancer. There are others who have searched for bacteria in these thromboses, and have also found them with fair frequency. Thus, Harris and Longcope<sup>3</sup> found bacteria in thirty-four out of forty-four cases of phlebitis, most of which were said to have been peripheral and of the so-called marantic type.

More recently deTakats<sup>4</sup> has gone a step further. Obtaining positive cultures in a goodly number of varicose veins removed at operation, he has formulated the concept of "resting infection" in varicose veins. According to this idea not only is varicose phlebitis an infective process, but the bacteria causing it may actually lie in varicose veins in a semidormant condition for long periods of time.

All these facts have gradually converted many physicians to the belief that all thrombophlebitis represents an infection of veins. In the meantime there has been rather strong evidence that nonsuppurative phlebitis is generally a bland process, and is rather due to physical factors such as slowing of the blood stream. Aschoff<sup>5</sup> is probably the most important contemporary proponent of this theory. This old theory gains modern support in the fact that several investigators have failed to find bacteria in most nonsuppurative phlebitis. Thus, Barker,<sup>6</sup> in a review of 166 cases of thrombophlebitis complicating infectious and systemic diseases, found that cultures were occasionally positive but usually sterile. Brown,<sup>7</sup> in a review of 87 cases of post-operative phlebitis, stated that no bacteria were found in those that were cultured. The reported results then, and my personal experiences, lead me to the conclusion that bacteria are only sporadically present in these cases.

So far as varicose phlebitis goes, my findings are somewhat paradoxical. While I have never been able to find bacteria by stain or culture of the clot or vein wall, I have nevertheless twice come upon gram-positive cocci in surgically excised saphenous veins, where there had been no suspicion of their presence. These patients did not have phlebitis, the wounds did not suppurate, nor was there evidence of any acute infection going on elsewhere in the body.

The histology of bland phlebitis differs also from that of the septic variety. There is usually very little cellular infiltration, and most of

the cells present are of the so-called "chronic inflammatory" or reparative type, that is, lymphocytes, plasma cells, and macrophages.\* The infiltration may be located for the most part around the vasa vasorum in the adventitia. Polymorphonuclear leucocytes are uncommon and few in number. This holds true even in those cases where the phlebitis is attended by clinical evidence of acute inflammation with much heat, swelling, and tenderness (Fig. 2).

There is a form of phlebitis in which it seemed more probable to find bacteria and acute inflammatory cells. I refer to a subacute phlebitis of small veins on the foot which occurs occasionally in patients with varicose veins, especially those which have followed a deep phlebitis ("ulcerating phlebitis").<sup>25</sup> The special features of this phlebitis are the location below either malleolus, the immediate dark pig-

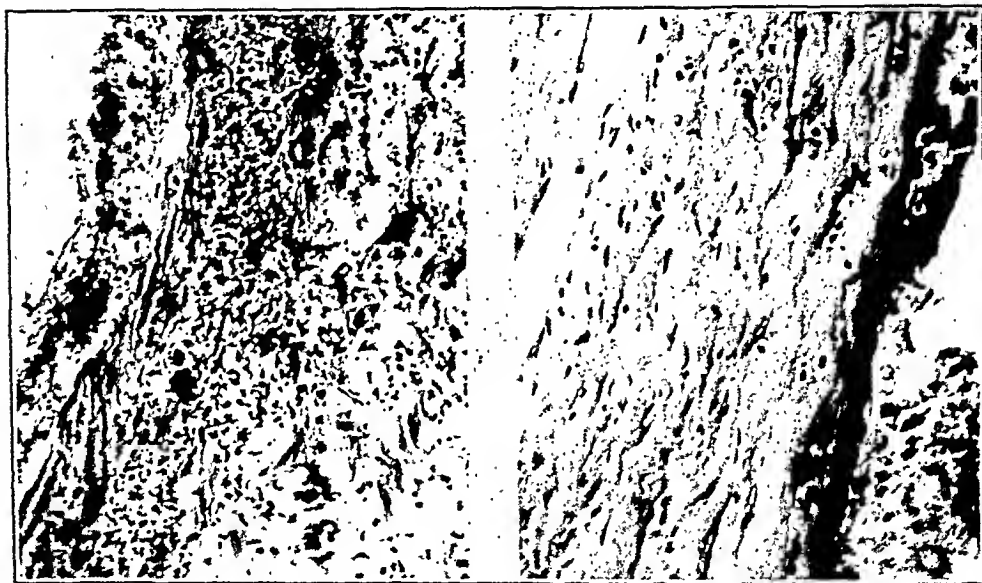


Fig. 1.

Fig. 2.

Fig. 1.—Pylephlebitis, a septic phlebitis, secondary to suppurative appendicitis. Section of a branch of the portal vein in the liver. Note the intensive acute inflammation, the wall of the vein being disrupted by polymorphonuclear leucocytes. Eosin and methylene-blue ( $\times 190$ ).

Fig. 2.—Phlebitis of a varicose vein, a bland phlebitis. Note the absence of inflammatory reaction. Hematoxylin and eosin ( $\times 190$ ).

mentation of the skin over the vein, and its immediate adhesion to it; and finally the almost irrevocable breaking down of this skin into a shallow, painful, and intractable ulcer. In two such instances I have performed a biopsy of the vein and skin in the pre-ulcerous stage. Bacteriological culture was made at the time of the biopsy, but no bacteria were obtained by either aerobic or anaerobic methods. Nor were bacteria seen in stained sections of the veins and skin. The histology of the tissue was surprisingly mild, an organizing thrombus was present, with very little cellular infiltration. What cells were present were chiefly lymphocytes and plasma cells.

\*The phlebitis of thromboangitis obliterans stands out as an exception.

Evidence of the bland nature of most phlebitis is also to be found in its clinical course. Though frequently mentioned, suppuration of a thrombus in bland phlebitis such as that of varicose veins, is rare. Indeed, I have never seen a single instance. It is possible that softening of the clot through autolysis, has occasionally been mistaken for suppuration. Here also it may be noted that while pulmonary embolism is quite as common as in the septic form, the resultant infarcts do not give rise to pulmonary abscesses. Moreover, varicose veins which are phlebitic may be injected or ligated with safety. In 63 cases treated by ligation and subsequent injection not a single instance of sepsis of the vein or septicemia has occurred.

In the face of the evidence at hand the words of Welch,<sup>8</sup> spoken in 1909, are still convincing; "Whilst we are justified in assigning a far more prominent place to the agency of micro-organisms and to primary phlebitis in the etiology of thrombosis than, until recent years, has been customary since Virchow's fundamental investigations, recent attempts to refer all thromboses formerly called 'marantic' to the direct invasion of micro-organisms, and to phlebitis, go beyond demonstrated facts."

#### SYMPATHETIC NERVE IRRITATION ACCOMPANYING PHLEBITIS

Certain phenomena occur in the course of phlebitis which can only be explained by a stimulation of the sympathetic nerve fibers of the extremity. The mechanism is not yet known, but it is clear that whether the reactions are due to direct, or to reflex stimulation of the efferent fibers, irritation of a vein is an adequate stimulus for these reactions.

The simplest of these reactions involves the veins themselves. In some individuals the puncturing of a vein in the forearm causes an immediate constriction of all the superficial veins of the limb, and it is common experience that a second successful puncture may be impossible for some minutes. This same phenomenon may be seen in the leg when an irritant solution is injected for the purpose of obliterating varicose veins. Such a constriction has been described in phlebitis by Leriche,<sup>22</sup> and by Ducuing,<sup>9</sup> who believed it is responsible for much of the pain. There is additional significance in this, however, as the contraction of the vein slows the blood stream and facilitates the progress of the thrombosis.

Aside from venous constriction, we may consider a group of reactions which, while originating within the veins, spread to affect other structures. The first of these is the augmentation of the pilomotor reflex. Ducuing<sup>10</sup> has remarked that the reflex may be diminished or increased. In practice the diminution of this reflex is not easily made out, but its increase is sometimes strikingly apparent. Thus when both the normal and the diseased limbs are exposed in the patient's



room, the skin of the phlebotic limb may show a pronounced goose flesh appearance, while the normal limb shows it not at all or very slowly. Again, abnormal promptness and intensity of the reflex may be shown by scratching the limb with the back of the nails, when broad streaks of goose flesh appear.

The second function of the sympathetic fibers which comes in evidence is that of local sweating. While ordinary generalized sweat-

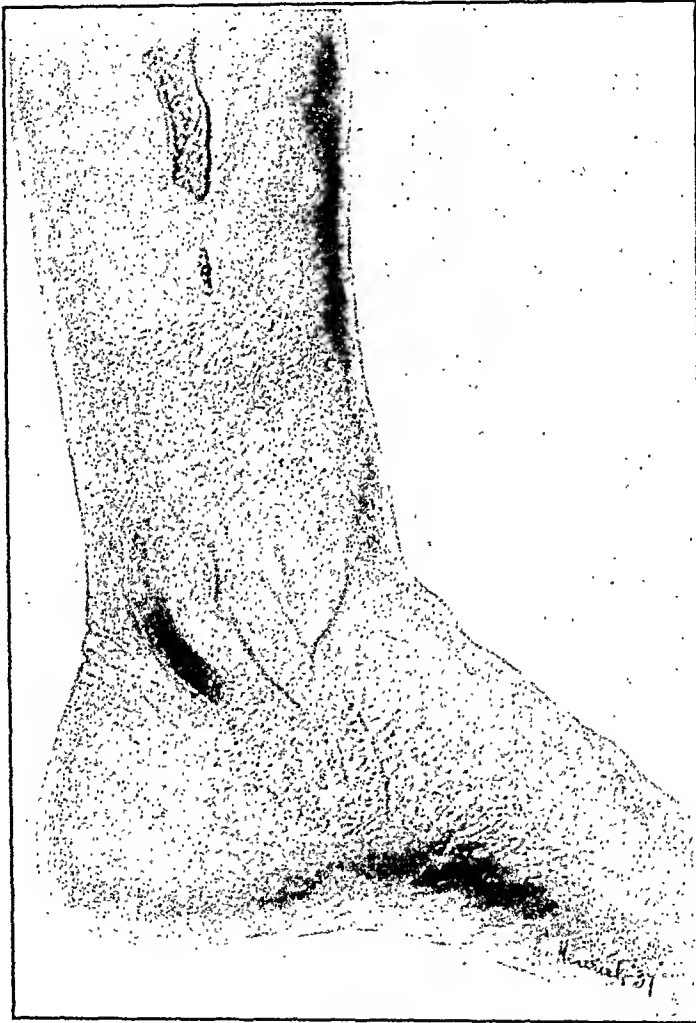


FIG. 3.—Localized sweating distal to tensely distended varices. The droplets were somewhat finer than shown.

ing occurs when the body is generally warmed, the local secretion can be seen even when the body is quite cold. This is the same type as that present in some neurological disturbances, in hyperhidrosis of the hands or feet and in those cases of vascular disease characterized by an increase in sympathetic tone. Well recognized examples of the latter are Raynaud's disease and thrombo-angiitis obliterans.

Localized sweating is frequent in the presence of vein irritation. It is best seen in cases of varicose veins that are large and tense or those

that are developing rapidly, as in pregnancy, and also in phlebitis of varicose veins. The sweat may only be apparent after the patient has been walking about or standing for some time. It appears as minute or medium-sized droplets arranged distal to the varices (Fig. 3). The droplets may be so small, indeed, as to be appreciated only on very close inspection or by feeling moisture on touching the leg. These droplets may increase in size, or make their first appearance, when the

Fig. 4.

Fig. 6.



Fig. 5.

Fig. 7.

Figs. 4 to 7.—Localized sweating in varicose veins and varicose phlebitis, outlined by starch iodine. Figs. 4 and 7 show proximal and distal areas. In each case the proximal area lies just below a zone of "phlebitis" induced by sclerosing injection. Fig. 5 is a case of varicose ulceration. Fig. 6 is of uncomplicated varices.

vein is punctured by a needle. The sweating is perhaps most apparent distal to areas of phlebitis in the varicose veins, whether it be spontaneous or induced by a sclerosing solution. To render the secretion conspicuous I have employed the starch iodine technique of Victor Minor.<sup>11</sup> A glance at the photographs of representative cases will show the fineness of the secretion and its localization into small areas (Figs. 4, 5, 6, 7). That the secretion is not necessarily an augmenta-

tion of the sweat in areas where it is normally high in amount, is shown by the fact that it is not confined to any one part of the leg or foot, but is called forth in any region distal to vein irritation.

Clinically the most important result of the sympathetic irritation is arterial constriction. It is quite commonly known that while, in phlebitis, the limb may be hot directly over the inflamed vein, it may be cold distal to it. Such a lowering of temperature can best be accounted for by a constriction of the arterioles.\*

Examples of more severe involvement of the arteries have also been mentioned many times. Authors have often spoken of the small pulses in phlebitis. This diminution has been confirmed by the oscilometer in several reported cases, and in some personally observed ones.

Finally, phlebitis may occasion a complete spasm of the major artery of the limb. Twenty-odd such cases have been reported, the majority in the French literature, with others in the German and American.<sup>13-20</sup> The events in the reported cases resemble those in a personally observed one.

#### CASE REPORT

Mr. O. S., was seen on the Third Medical Service of the Boston City Hospital at the request of Dr. Cadis Phipps. This man, a forty-six-year-old carpenter, entered the hospital on July 19, 1935, for treatment of a pulmonary embolism resulting from a deep phlebitis of the right leg. Within the next two weeks, the phlebitis ascended to involve the right femoral, then the right iliac vein. On August 6, 1935, a series of events took place which were carefully observed and recorded by Dr. J. C. Drucker, the House-Officer on service. I quote from his notes:

"August 6, 1935, the patient was seen at 9:00 A.M., and stated that he felt well except for some pain along the medial side of the left thigh. This pain in the left thigh was present for the first time. About 11:30 A.M. the patient was seen again and complained of more pain in this area and there was slight cyanosis of the left lower leg. The pulsation of the femoral artery was present and was of good volume. The patient also complained of some additional pain in the lower right chest (site of previous infarction). Examination of the chest showed no change from what had been heard previously; namely, diminished breath sounds at the extreme lower part of the right lung, posteriorly, and bronchial breathing which was distant above; and also a short terminal inspiratory friction rub anteriorly.

"At about 3:45 P.M. the patient complained that he was unable to feel any sensation in the left leg from the knee down and there was pain above this area. He complained also that he was unable to move the foot or toes. At this time, the leg from the hip down resembled in color an arm which has had a tourniquet applied in the tourniquet test for scarlet fever. The leg was cold, dry, and anesthetic up to the knee, while above, it was hyperesthetic. There were no pulsations made out in the femoral, popliteal, posterior tibial, or dorsalis pedis arteries.

"At about 6:00 P.M. hot water bottles were applied to the leg, and at 7:30 P.M. the condition of the leg from the knee down had changed considerably. The patient stated that ten minutes after the heat was applied, sensation had returned in the lower leg and in about three-quarters of an hour he was able to move the foot

\*Audler<sup>12</sup> has found in these cases a more rapid absorption rate in the McClure-Aldrich test.

and toes. The leg was pink in color, sensation had returned, and there were good pulsations in the femoral, dorsalis pedis, and posterior tibial arteries. The femoral vein was palpable as a tender induration. Two enlarged veins were seen on the left flank which had definitely not been visible before."

*Comment.*—This patient showed temporarily all the signs of an occlusion of the femoral artery; namely, the disappearance of the femoral pulse and the pulses below, the cold white skin, the anesthesia below and the hyperesthesia above, and the loss of muscle power. The diagnosis at the onset of this episode seemed surely to be either embolism or thrombosis of the femoral artery, yet with the application of heat, all the signs wore off and the pulses returned. Within a few hours the diagnosis of iliac and femoral phlebitis was definite. The limb subsequently went through the usual sequence that one finds in iliac phlebitis. There was edema from the buttock down; there was enlargement of the superficial veins of thigh and abdomen; and there was the tender induration of the femoral vein of the thigh. The edema slowly subsided during the patient's stay in bed. Later, when the patient was up and about, the edema increased temporarily but soon became less again.

By the latter part of September, 1935, there was but little edema and the surface veins of the thigh and abdomen were beginning to diminish in size, indicating that the clot was being canalized. The leg showed not the slightest evidence of arterial impairment. All the pulses were of full volume; an arteriogram showed that there was a normal lumen in both the main and deep femoral arteries; and the oscillometric readings (Pachon) were quite normal. The actual readings were as follows:

|             | MEAN ARTERIAL PRESSURE<br>IN MM. OF MERCURY | OSCILLOMETRIC<br>UNITS |
|-------------|---|------------------------|
| Right thigh | 120   | 6.5                    |
| Left thigh  | 120   | 6                      |
| Right leg   | 100   | 5                      |
| Left leg    | 100   | 5                      |

In cases of embolism or thrombosis of the femoral artery, one must certainly have rare good fortune to observe the spontaneous reappearance of all the pulses of the limb and to find that the objective measurements of the calibers of the vessels are normal and exactly equivalent to the opposite extremity. As a matter of practice, such an outcome is but rarely observed, even after a successful embolectomy. One cannot escape the conclusion that this patient had no organic obstruction to the arteries at all, but that his arterial occlusion represented a temporary, complete spasm of the femoral artery, incident to the start of the phlebitis in the left iliac or femoral vein.

The picture then closely simulates arterial embolism. The femoral artery is the most frequently involved, and the spasm is secondary to

thrombophlebitis of the femoral or iliac vein. There is a sudden severe pain in the course of the artery, then in the entire leg. The femoral pulse is absent, the limb painful, cold, and paralyzed. After some few hours the attack may wear off spontaneously, or as has rarely happened, actual thrombosis may occur.

The arteriospasm may occur after the phlebitis is quite evident, but it usually happens so early that the diagnosis may be difficult to establish. Thus, while the telltale edema and cyanosis of phlebitis may be present, ordinarily the only hint of primary venous involvement is a slight cyanosis of the thigh above the ischemia of the foot and leg, and a slight dilatation of the surface veins of the thigh and abdomen.

In some of the earlier reports it is likely that there were included instances of a true arteritis by extension from pelvic sepsis, or simultaneous phlebitis and arteritis of thrombo-angiitis obliterans type. In many, however, there is no doubt but that there was merely a spasm of the artery.\* Several of the reported cases were operated on for the suspected embolism. In all these the artery was found contracted and pulseless but the pulse reappeared immediately after the artery was freed from its sheath. In other patients arteriograms were made and the arteries found to be patent. Some of the patients died from pulmonary embolism and autopsy revealed patent arteries. Finally, gangrene occasionally supervened, and examination of the amputated extremities revealed normal arteries.†

#### CHANGES IN THE VENOUS VALVE

Apparently the fact that phlebitis damages the venous valve was first appreciated by Homans,<sup>26</sup> although he did not publish demonstrations of this damage. Recently, with Jesse Edwards, I have completed a detailed study of this effect. We made histological examinations of the valves in spontaneous phlebitis in the human and in experimental chemical phlebitis in the dog. This is reported elsewhere,<sup>27</sup> but it is of interest here to state briefly our findings.

When complete thrombosis occurs the forces of organization and recanalization pay little respect to the cellular nature of the valve, but treat it in the same way as they do the rest of the venous content, that is, the clot. In other words, the valve cusp is immediately subjected to disrupting forces. At first these forces consist of a growth

\*The exact mechanism for the production of the arteriospasm is not known. Leriche, <sup>25</sup> Homans,<sup>26</sup> and Jennings<sup>28</sup> have surgically explored the vascular sheath of the iliac and femoral vessels in some cases of phlebitis, and have occasionally found a nonpurulent plastic inflammation involving the adventitia of artery, vein and lymphatics, all with apparently equal virulence. Given such an inflammation, the spasm of the artery is explainable by direct irritation. In most instances, however, the vein is involved by itself and the artery is reflexly contracted. The possible path of such a reflex has been touched upon by Cornell, Mosinger, and Audler,<sup>29</sup> but has not yet been demonstrated.

Since this paper was written, de Takats (Arch. Surg. 31: 939, 1927) has reported vasospasm originating from phlebitis and other lesions and gives a fine discussion of the probable reflex arc.

†There are several reported cases of gangrene in the course of massive venous thrombosis, in which the arteries were demonstrated to be patent. In these cases, besides the extensive venous obstruction two other factors seem responsible, namely, spasm of the arteries and superimposed infection.

of capillaries through the base of the cusp and the exudation of reparative cells. But the fibroblasts, as they grow into the clot, cut across the cusp as well and divide it into fragments. At least some recanalization always occurs and the cusp is now more seriously fragmented by the new blood channels which run through it, and push its fragments apart. The cusp soon completely disappears. Occasionally the valve is open at the moment of thrombosis and its cusps therefore lie close to the vein wall. In such a case its fragmentation may be slight, but the cusp lies imbedded in the organizing thrombus and

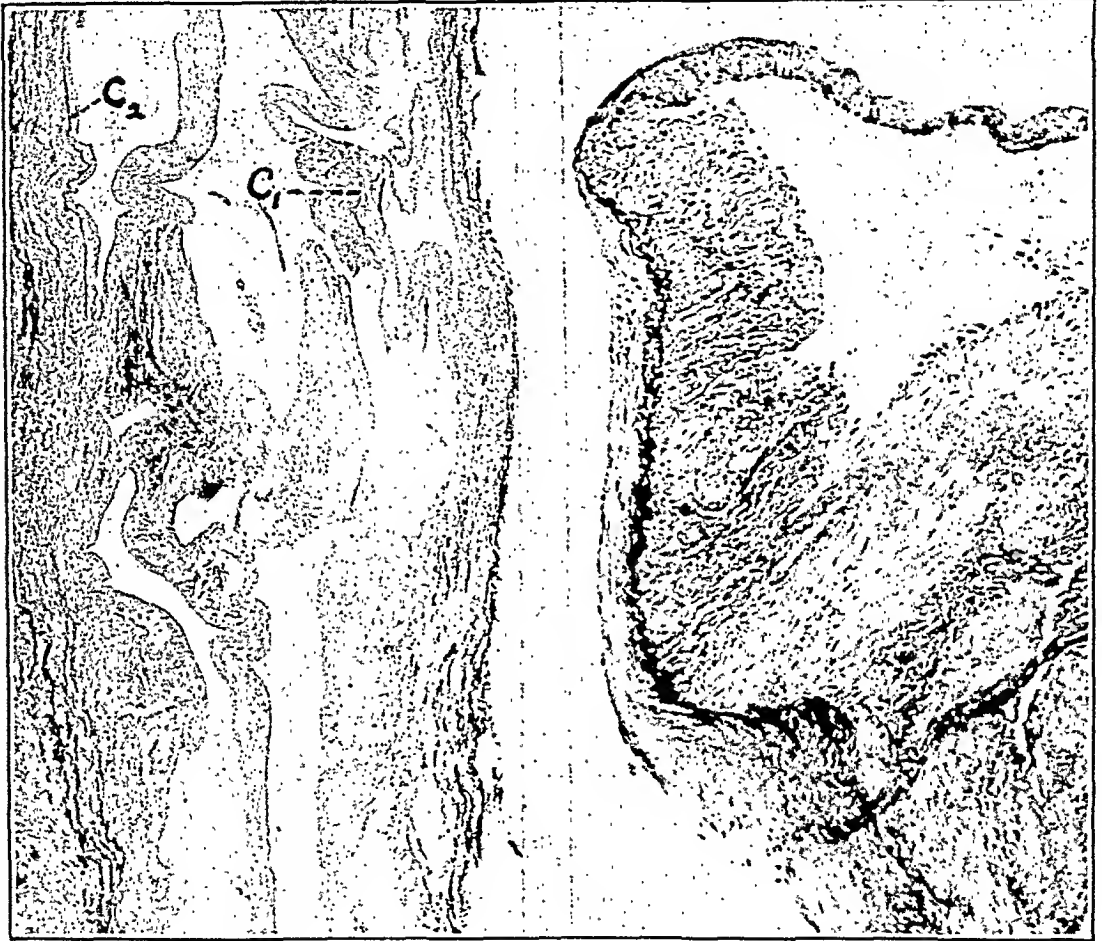


Fig. 8.

Fig. 9.

Fig. 8.—Destruction of the venous valve by complete thrombophlebitis. Longitudinal section of dog's femoral vein at valve site, four months after artificial phlebitis. Recanalization is not yet complete but it has already broken up the thrombus leaving trabeculae crossing the lumen. In one of these, at C-1, is a small piece of elastic tissue, a remnant of the previously existing valve. At C-2 is a longer strip representing the second cusp imbedded in the new thickened intima. The dark areas in the heavier trabeculae below are nuclei and pigment. Verhoeff's elastic tissue plus van Gieson's stains ( $\times 23.5$ ). (From Surg. Gynec. & Obst. 65: 310, 1937.)

Fig. 9.—The production of venous stenosis and regurgitation by incomplete thrombophlebitis. Longitudinal section of single cusp from human saphenous vein involved in spontaneous phlebitis (operative specimen). The structure is thickened and shortened by the addition of connective tissue, especially on its sinus side. Here the connective tissue effects an adhesion of cusp to vein wall. Compare the thickness of the diseased proximal half of the cusps to the normal thin distal half. Verhoeff's elastic tissue plus van Gieson's stains ( $\times 92$ ).

when recanalization is complete we find it incorporated in the now thickened intima. In any event, complete thrombosis always results in the actual or functional disappearance of the venous valve (Fig. 8).

Incomplete or parietal thrombosis, as is well known, has a predilection for attacking valve sites. The earliest thrombi are seen in the valve sinuses, where subsequent organization produces a pad of tissue which narrows the lumen of the vessel, and does not allow complete lateral excursion of the cusp. If the valve is open at the moment of thrombosis, with the cusp lying close to the vein wall, this organization incorporates it and it disappears in the new intima. If the valve is closed and the cusp lies in the center of the lumen, some of it will be bound down by the connective tissue formation in the sinus, and the remainder thickened by a proliferation of connective tissue along its two surfaces. This proliferation in the lateral commissure of the valve may also cause the two cusps to become adherent to each other.

The end-result of incomplete thrombosis is, then, a shortened, thickened, adherent cusp of little excursion (Fig. 9). These stubby, rigid valves look altogether different from the veil-like normal ones. The diseased valves resemble the mitral valve which has been involved in a rheumatic endocarditis, and we believe that the term "stenosis and regurgitation" may equally well be applied to both.

In the case of complete thrombosis of a main trunk we may see an incomplete thrombosis extending into the mouths of its tributaries. Here the valves which guard these mouths will be involved. The involvement may be of the type above described under the term "incomplete thrombosis" or there may be a special form of damage. In this latter instance the cusp as it opens into the lumen of the main trunk is caught in the thrombus of the main trunk. Here it may be destroyed if it is entirely embedded in the clot, or it becomes adherent along its free edge if it merely touches the clot. This is the type of involvement which destroys the function of the valves in the perforating vessels of the leg when a deep thrombosis occurs.

The destruction of the venous valve or the production of a venous stenosis and regurgitation helps to clarify the disability occurring after phlebitis. Reference is of course made to the so-called "post-phlebitic" evidences of inefficient return. Difficulty with the venous return exists whether or not the vein has recanalized. If the lumen is adequately restored the valves are absent or crippled. If it is not adequately restored, the blood flows in collateral channels, where, as we have indicated, the valves become incompetent due to the dilatation of these channels.

#### THERAPEUTIC INFERENCES

The management of phlebitis is undergoing considerable change. For the author, the essentially bland nature of the phlebitis of varicose veins and the almost absolute rule that both the varices and the phlebitis will recur after the acute process is over, have prompted the immediate treatment of these patients by ligation of the great saph-

nous vein followed by small injections of sclerosing solution. Post-operatively the patient is treated in the same ambulatory fashion as any uncomplicated case of varicose veins. At the time of the first observation the thrombosis may make it impossible to determine whether or not the vein was valveless; but one may rest assured that it will be so when the recanalization has occurred. Therefore, whether or not the veins are surely varicosed, they are treated the same way, with the exception of cases of migrating phlebitis. These are treated conservatively because thrombo-angiitis obliterans is likely to be present. No pulmonary embolism or other untoward reaction has been seen in the 63 cases thus treated.<sup>28</sup>

The fact that phlebitis produces an irritation of the sympathetic fibers of the limb, leads one to inquire how this may be overcome and whether by so doing the patient will be benefited. Leriche and his associates<sup>29, 30</sup> have performed novocaine infiltration of the lumbar ganglia with immediate cessation of pain and subsidence of the edema. In the chronic postphlebotic edemas this procedure was only of temporary value. Other French workers have obtained good results by repeated subcutaneous injection of acetylcholine. The sympathetic release so obtained by these or any methods is undoubtedly responsible for the improvement noted. The increase in arterial flow thus obtained produces a greater velocity of flow in the veins, increasing their nourishment and diminishing the chances for propagation of the thrombus. If it is also true that venous spasm is a concomitant of phlebitis, its relief by sympathetic release will again increase the venous flow and inhibit the spread of the thrombosis. Appreciating the presence of sympathetic irritation should make us question the use of cold applications in phlebitis. The use of the ice pack has already fallen into disrepute with many, because it promotes thromboses and devitalizes tissue. Now we have this additional reason for condemning it.

Though the above methods of securing vasodilatation deserve extension, I have so far been content to use local warmth in the form of a heated cradle, or as hot compresses, while in the severer cases I have used parenteral foreign protein. Such therapy, as you know, diminishes the coagulability of the blood and lowers the sympathetic tone. Striking results have followed the use of intravenous typhoid vaccine, or in sicker patients the intramuscular injection of sterile milk products.

Of late the matter of rest and exercise in phlebitis has also attracted some attention.<sup>31, 34, 32</sup> Previously, patients with either superficial or deep phlebitis were kept in bed for weeks or months in order to minimize activity of the limb and thus cut down the chances for pulmonary embolism. The thrombus at the original site of the phlebitis is more or less fixed because of the changes in the vein wall, antecedent or secondary, but there is frequently a propagation of



softer more friable clot attached to either end of the original thrombus. This clot is due to the stagnation of the blood and has therefore been called a "stagnation thrombus." These propagated clots are not necessarily in contact with vein wall all along their course, and no amount of time may suffice for them to become firmly attached. Sooner or later the patient must move his limbs, in bed or out, and if stagnation thrombi have formed they are practically sure to break off and to give embolism.

It has been amply demonstrated, in superficial phlebitis at least, that immediate exercise of the limb will prevent the formation of this secondary clot from which emboli arise. Deutsch, in 1929,<sup>33</sup> and Jaeger, in 1930,<sup>34</sup> reported six hundred, and one hundred cases, respectively, of superficial phlebitis of the leg, treated merely by bandaging and forced to remain ambulatory. In these consecutive cases not a single pulmonary embolism resulted.

Confronted with a deep phlebitis, it is more difficult to fly in the face of custom and to prescribe exercise. If the phlebitis has lasted for some days with the limb at rest, stagnation clots are already apt to be present. Certainly at this stage very active exercise is dangerous, but it seems logical that there is even more chance for pulmonary embolism if the stagnation is continued, than if regular gentle movement be instituted. If the patient has survived a single pulmonary infarct, he may die from a second or third. For this reason, whenever feasible, the main venous trunk should be ligated after pulmonary embolism.

If the phlebitis is fresh, my feeling is that gentle exercise of the limb should be started at once and be increased daily. The results in several cases thus treated have been gratifying. Pulmonary embolism is, however, such a serious accident, that a large series of phlebitides treated both with and without exercise will have to be compared before this can be laid down as the best method of procedure.

#### REFERENCES

1. Virchow, R.: *Zur Geschichte der Thrombose*, Wien. med. Wehnschr. 7: 217, 1857.
2. Vaquez, H.: *La Thrombose Cachectique*, Thèse, Paris, 1890.
3. Harris and Longcope: Quoted by Welch.<sup>8</sup>
4. deTakats, G.: "Resting Infection" in Varicose Veins: Its Diagnosis and Treatment, *Am. J. Med. Sc.* 184: 57, 1932.
5. Aschoff, L.: *Thrombosis*, in *Lectures in Pathology*, New York, 1924.
6. Barker, N. W.: *Thrombophlebitis Complicating Infectious and Systemic Disease*, *Proc. Staff Meet. Mayo Clin.* 11: 513, 1936.
7. Brown, G. E.: *Post-operative Phlebitis. A Clinical Study*, *Arch. Surg.* 15: 245, 1927.
8. Welch, W. H.: *Thrombosis*, in *Allbutt and Rolleston's System of Medicine*, Vol. VI, London, 1909.
9. Ducuing, J.: *Quelques Signes Neuro-Sympathique des Phlébites Post-opératoires. Leur Valeur dans le Diagnostic Précoce de cette Affection*, *Prat. méd. franç.* 14: 222, 1933.
10. Ducuing, J.: *Le Rêflexe Pilo-moteur dans le Diagnostic Précoce des Phlébites Post-opératoires*, *Bull. Soc. d'obst. et de gynéc.* 22: 255, 1933.

11. Minor, V.: Ein neues Verfahren zu der klinischen Untersuchung der Schweissabsonderung, *Deutsch. Ztschr. f. Nervenhe.* 101: 302, 1928.
12. Audier, M.: Le Test D'Aldrich et McClure dans le Diagnostic des Phlébites des Membres, *Gaz. méd. d. France*, p. 18, April 1, 1934.
13. Homans, J.: The Operative Treatment of Phlegmasia Alba Dolens, *New England J. Med.* 204: 1,025, 1931.
14. Homans, J.: Thrombophlebitis, in *Nelson's Surgery*, Vol. III.
15. Låwén, A.: Arteriospasmus bei akuter massiver Thrombose der V. femoralis, *Zentralbl. f. Chir.* 56: 1,681, 1934.
16. Wertheimer, P., and Fric, P.: Thromboses Veineuses, Obliterations Artérielles, et Gangrène des Membres, *Presse méd.* 43 (1): 1,004, 1935.
17. Audier, M.: La Symptomalogie Artérielle dans le Phlébites des Membres et de leurs Sequelles, *Progrès. méd.*, May 4, 1935, pp. 729-738.
18. Audier, M.: Thromboses Veineuses Aiguës simulant L'Embolie Artérielle des Membres, *Paris méd.* 1: 384, 1936.
19. Gutzeit, R.: Brand durch Venensperre, *München. med. Wehnsehr.* 83: 1,628, 1936.
20. McKechnie, R. E., and Allen, E. V.: Sudden Occlusion of the Arteries of the Extremities, *Surg. Gynec. & Obstet.* 63: 231, 1936.
21. Leriche, R.: Essai de Traitement Chirurgical des Suites Eloignées des Phlébites du Membre Inférieur, *Presse méd.* 27: 309, 1923.
22. Leriche, R.: Traitement Chirurgical des Suites Eloignées des Phlébites et des Grands Oedemes non Médicaux des Membres Inférieurs, *Bull. et mêm. Soc. nat. de chir.* 53: 187, 1927.
23. Homans, J.: Phlegmasia Alba Dolens and the Relation of the Lymphatics to Thrombophlebitis, *AM. HEART J.* 7: 415, 1932.
24. Jennings, J. E.: Choked Leg, *Ann. Surg.* 98: 928, 1933.
25. Cornil, L., Mosinger, P., and Audier, M.: Les Interrelations Arterio-Veineuses Pathologiques des Membres, *Presse méd.* 22: 411, 1937.
26. Homans, J.: The Operative Treatment of Varicose Veins and Ulcers, Based Upon a Classification of these Lesions, *Surg. Gynec. & Obstet.* 22: 143, 1916.
27. Edwards, E. A., and Edwards, J. E.: The Effect of Thrombophlebitis on the Venous Valve, *Surg. Gynec. & Obstet.* 65: 310, 1937.
28. Edwards, E. A.: Phlebitis of Varicose Veins. To be published.
29. Leriche, R., and Kunlin, J.: Traitement Immédiat des Phlébites Post-Opératoires par L'Infiltration Novocainique du Sympathique Lombaire, *Presse méd.* 76: 1,481, 1934.
30. Kunlin, J., and Lueinesco, E.: Résultats du Traitement Immédiat des Phlébites Post-Opératoires et Variqueses par L'Infiltration Novocainique du Sympathique Lombaire. Cinq. Nouvelles Observations, *Bull. et mêm. Soc. nat. de chir.* 61: 965, 1935.
31. Kilbourne, N. J.: Phlebitis. Its Treatment, *California & West Med.* 45: 176, 1936.
32. Ochsner, A.: Thrombophlebitis. In *Dean Lewis' Practice of Surgery*, Vol. XII.
33. Deutsch, H.: Zur Behandlung der akuten lokalisierten Phlebitis der unteren Extremität, *Wien. klin. Wehnsehr.* 42: 1,162, 1929.
34. Jaeger, F.: Zur Behandlung der Thrombose und der Thrombophlebitis, *Zentralbl. f. Chir.* 57: 1,921, 1930.

## THE PATHOLOGICAL BASIS FOR INTERMITTENT CLAUDICATION IN ARTERIOSCLEROSIS\*

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THE symptom complex of intermittent claudication, or exercise pain, which may occur in any type of obliterative or obstructive arterial disease of the lower extremities, is a common though by no means a constant concomitant of arteriosclerosis. In some cases it occurs before any other definite vascular symptom is manifest. In other cases gangrene of the toes or the foot supervenes from gradual arterial occlusion, or from trauma and infection, without the appearance at any time of the syndrome of intermittent claudication.

Arteriosclerosis is a disease in which vasospasm and infection are absent, at least from the initial picture, and in which the basic pathological change is a purely obliterative process affecting the arteries. Why intermittent claudication should be present in some cases and not in others, or, indeed, why it should occur at all, is not clearly understood. It is generally believed that its basic cause is the diminution in the blood volume which reaches the involved part as the result of arterial obstruction, but thereafter the theories of its causation vary. Lewis,<sup>1</sup> in an excellent monograph entitled "Vascular Disorders of the Limbs," advances the idea that the cause is obstruction of the large vessels of the extremities. Hermann,<sup>2</sup> on the other hand, recognizes two forms of obstruction of the arterial supply which might produce it, obstruction of the large trunks and obstruction of the arterioles. The only work on record, so far as we know, which concerns the anatomical distribution of the points of obstruction or obliteration in this symptom complex was done by the author,<sup>3</sup> and records the vascular pattern in 12 cases of intermittent claudication on an arteriosclerotic basis.

The valuable experimental work of Barney Brooks<sup>4</sup> has thrown considerable light upon the altered physiology produced by obstruction of the large arteries. Three important changes occur, he says: The blood volume flow is diminished, the intravascular pressure is decreased, and the pulse pressure is markedly diminished or disappears entirely. Brooks found, furthermore, that even a slight decrease in the flow of blood to the extremity produced a fatigue complex comparable to intermittent claudication. He therefore concluded that the diminution in the blood volume was the main factor in the production of intermittent claudication.

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Read before The American Heart Association, section for the study of the peripheral circulation, at Atlantic City, N. J., June 7, 1937.

By means of arteriography we have been able to carry Brooks' observations farther. All our studies show that when the large arteries of the extremities are suddenly obstructed, whether by trauma, severance of the vessels, or thrombosis, there is a diminution in the number of functioning smaller muscular arteries and their terminal branches, and, undoubtedly, closure of many of the arterioles and capillaries in which these arteries terminate.

Before going into further detail on this subject, it may be well to outline briefly our experience with arteriography, by which method, during the past five years, we have had the opportunity of studying many types of peripheral vascular diseases of the lower extremities. The technique for visualizing the vessels of the lower thigh, popliteal region and upper two-thirds of the leg we have outlined in other communications<sup>5, 6, 7</sup> and shall not repeat here. At the beginning of our work, we made, for purposes of comparison with pathological cases, a series of arteriograms of the blood supply in normal cases in various age groups, and by the study of these arteriograms we established certain criteria for the normal blood supply:

1. The femoral, popliteal, and tibial arteries with their branches present a smooth, regular course. They decrease in size as they progress toward their termination, but at no point is there any narrowing of the channel by plaques or other types of obstruction.

2. The large muscular branches are given off uniformly from the large trunks and are long and evenly distributed.

3. The small muscular branches are numerous and are given off at regular intervals from the larger branches. They terminate in fine twigs, which in turn supply even finer twigs to all parts of the soft tissue. The whole process may properly be described as arborization, and the picture is precisely the picture seen in the branches of a tree. All parts of the muscular tissue are uniformly supplied, and the terminal twigs literally cover the entire muscular area (Fig. 1A).

4. The hallmarks of a normal vascular supply may be set down as smoothness of contour, regularity of pattern, and adequacy of size and distribution.

In arteriosclerosis there are several distinct patterns of arterial obliteration, which vary widely in extent. In one group of cases there is a gradual narrowing of the large trunks, with a variation in the development of the collateral blood supply. Sometimes the development of new vessels has kept pace with the obliterative process in the large trunks, so that obstructive symptoms never develop: when the large trunks have been completely occluded, an adequate collateral circulation has taken over their function. Sometimes the obliterative process outstrips the development of the collateral circulation and serious obstructive symptoms are manifest early. At other times the collateral circulation takes the form of large, tortuous vessels, which seem to carry an adequate volume of blood to the extremity, yet which actually do not,

as serious obstructive symptoms promptly supervene. In another group of cases the large trunks may remain patent and the obliterative process may be confined chiefly to the smaller vessels; in such cases serious symptoms of obstruction are always present. In the final group of cases the obliterative process involves uniformly the entire arterial system of the extremity, and marked symptoms are of course inevitable.

Our present communication is based upon an analysis of the vascular changes, as demonstrated by arteriography, in a series of 41 cases in which intermittent claudication was the outstanding symptom, and in all of which the basic vascular pathology was arteriosclerosis. In most cases other signs and symptoms of vascular degeneration were present in addition to the exercise pain, and in eight cases gangrene of one or more toes was also exhibited. There was a wide variation in the duration and severity of the exercise pain. In some instances it appeared when the patient had walked less than a block, while in other instances the patient could walk as much as ten blocks before it appeared. In all patients the pain was typical, in all it affected the calf muscles, and in almost all it was bilateral. The period of rest necessary for relief varied from one and one-half to fifteen minutes.

The age range in this group was from thirty to seventy-five years, with the average age 51.4 years. White males predominated, followed in order of frequency by white females, negro females, and finally negro males. The series of cases is obviously too small to make deductions from these findings of any value.

All the pictures were made in the basal state, that is, during a rest period, and at room temperature, in order to rule out the effect of exercise or of increased local temperature on the vascular picture. All pictures were taken so that the entire pattern was visualized at the site at which pain was most pronounced. In other words, all the arteriograms showed the lower femoral and popliteal arteries and the arteries of the upper two-thirds of the leg. The pictures were studied first by normal standards, and then in comparison with each other, in order to determine both variations from the normal and changes in the vascular pattern common to all cases. To simplify the comparisons we divided the arterial system of the extremity into its component parts, these including: the lower femoral artery; the popliteal artery; the anterior tibial artery; the posterior tibial artery with its main branch, the peroneal; the large muscular branches; and the secondary muscular branches with their terminal twigs, which latter were studied with the aid of a magnifying glass.

Our findings fall into three distinct groups, some of which are further subdivided:

1. In 21 cases there was complete obstruction at some part of one of the large trunks;

- A. In five cases the lower femoral artery was obstructed. In four of these the lumen of the popliteal artery was narrowed, but the vessel

filled from a collateral supply; in the other case the obstruction extended through the popliteal artery. In all five cases the tibial arteries and the peroneal were patent and were filled from collateral vessels.

B. In twelve cases the popliteal artery was obstructed. In eight of these cases the upper portions of the posterior and of the anterior tibial artery were obstructed, as was the popliteal artery; in the other four cases these arteries were patent throughout. The tibial vessels were usually filled at a lower level by communicating branches.

C. In four cases there was a marked narrowing of the femoral and the popliteal arteries, with obstruction of the anterior tibial artery in five cases and of the posterior tibial and the peroneal arteries in one case.

2. In six cases there was a definite, marked narrowing of the lower femoral and the popliteal arteries, although in no instance was the obstruction complete. Sometimes the constriction was uniform, sometimes large atheromatous plaques protruded into the lumen, producing almost complete obstruction at these points.

The collateral circulation in these cases varied considerably. Sometimes several large collateral vessels originated above the obstruction of the popliteal artery and extended well down into the calf muscles. Sometimes the attempt at the formation of a collateral circulation was very slight. Sometimes collateral vessels extended the whole length of the leg and undoubtedly carried a sufficient volume of blood to the extremity; the muscle fibers, however, did not receive adequate nutrition, since the new collateral vessels provided no small muscular branches.

In all the cases in which one or more of the large trunks was completely obstructed or markedly narrowed, it was striking to note the diminution in the number of functioning muscular branches. This was particularly evident in the smaller branches, and some arteriograms showed large areas of muscle devoid of any small muscular branches.

3. In fourteen cases the large vessels of the extremity were patent throughout their course and their lumina were within normal range. Sometimes their course was tortuous, but there were no points of constriction or obstruction. Here the defect was in the small muscular branches, which were few in number, irregularly distributed, and considerably shorter than normal. There was also a marked diminution in the number of fine terminal branches given off from the muscular branches. This group of cases, we feel sure, is usually described as arteriolosclerotic, and it is important to note that the obstruction involves the small muscular branches, as well as the arterioles and capillaries.

It is clear from what has been said that the single abnormality common to all these cases is the obstruction of the small muscular branches with their fine terminal twigs (Fig. 1), or, to put it differently, the loss of the arteriolar and capillary arborization by means of which the muscle fibers are supplied. This is the only abnormality present in the third group of cases, and it is present also in the first two groups, in

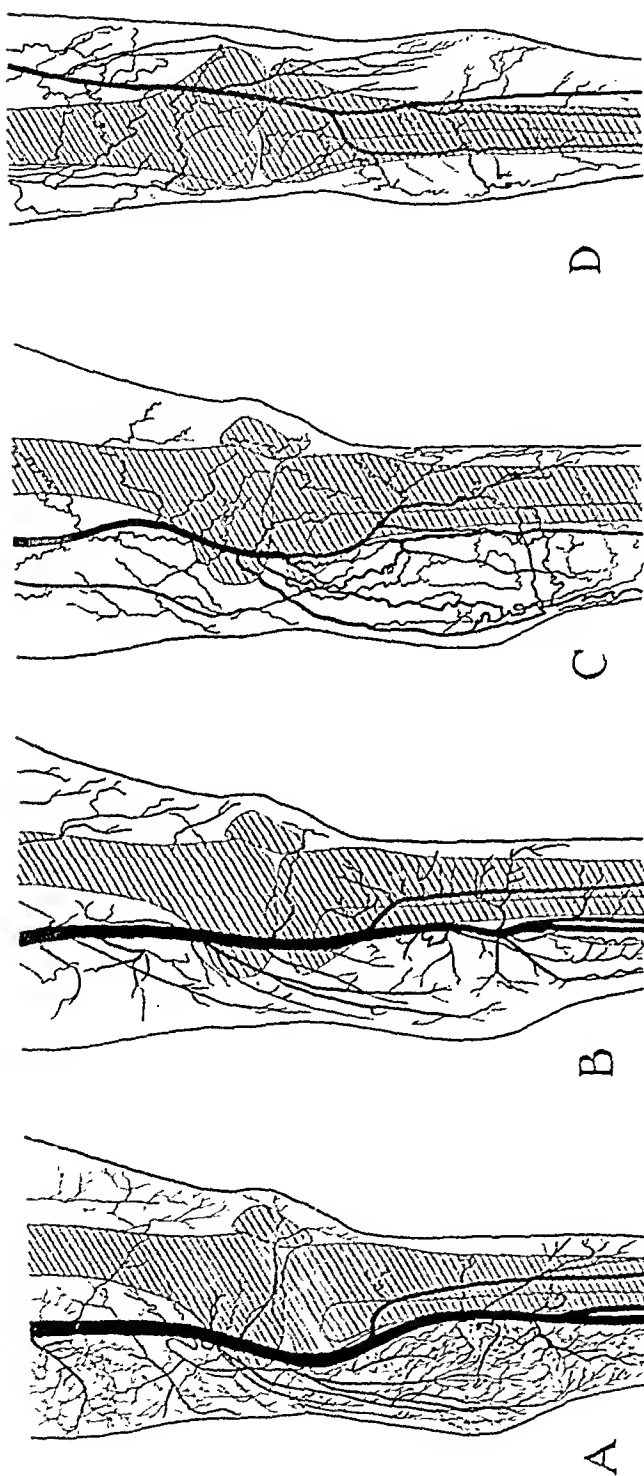
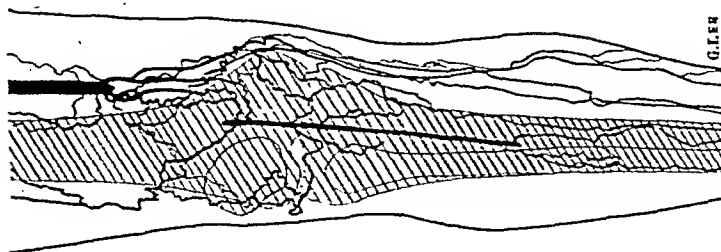
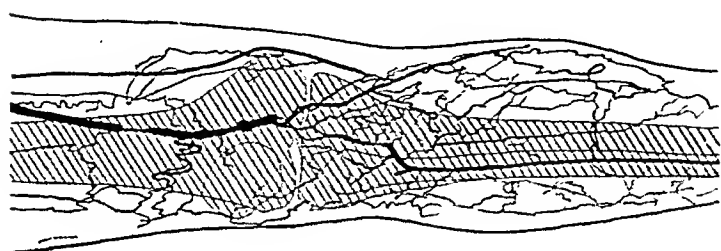


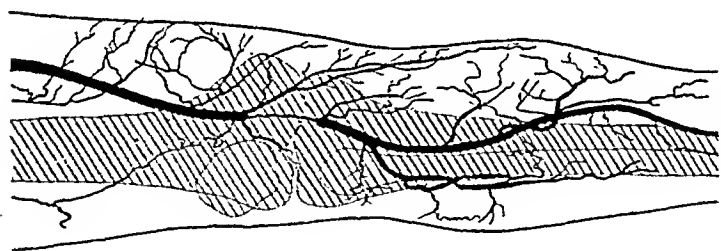
Fig. 1.—Ten drawings from arteriograms of the lower thigh and upper two-thirds of the leg. A shows the normal arterial pattern and B, C, D, E, F, G, and H show variations from the normal in arteriosclerotic types of intermittent claudication. Note the uniform distribution of the smaller nutritive arteries in the normal pattern (A), and the decrease in number and irregular distribution of these vessels in pathologic cases.



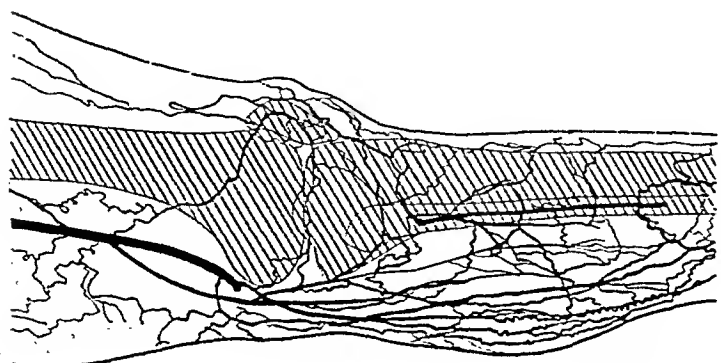
H



G



F



E

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which there is complete obstruction or some degree of narrowing of the large trunks. Our studies show that the obliterative process may affect all the muscles of the extremity, or a single muscle, or even an isolated portion of some muscle.

Further proof that it is the obliteration of these fine vessels which is responsible for the impairment of muscle function is supplied by repeated arteriographic studies on patients whose intermittent claudication has improved under treatment. In such cases we have never noted

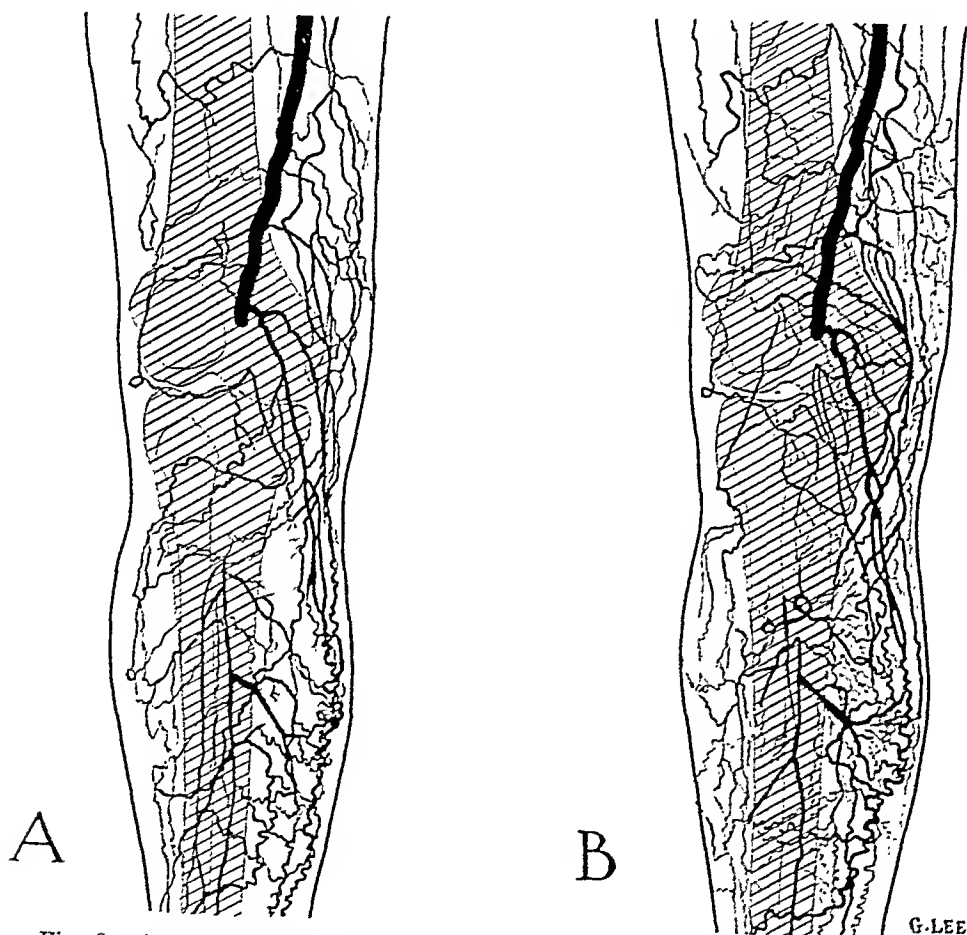


Fig. 2.—A. Case of intermittent claudication before treatment, showing obliteration of the popliteal artery. Note the extensive development of the collateral circulation and the diminution in the small muscular branches. B. The same case after relief of the intermittent claudication by treatment with alternate suction and pressure therapy. Note the marked development of small muscular branches and terminal twigs.

any change in the large vessels, but we have invariably noted an increase in the number and size of the fine terminal arteries, as well as an improvement in their distribution (Fig. 2A and B). We have also seen cases in which arteriosclerotic gangrene of the foot was present, with complete obstruction of the popliteal artery (Fig. 3), but in which exercise pain was absent because, we believe, the development and distribution of the small muscular branches was adequate.

The vascular patterns in intermittent claudication which we have outlined are the patterns seen during the resting stage, at which time there is no pain. It is now necessary to consider the changes which occur in the arterial supply during exercise, when there is pain.

In a previous communication<sup>3</sup> on this subject we have shown that during the exercise or pain period in arteriosclerotic intermittent claudication there is actually more blood flowing to the extremity than there is during rest; the increased volume flow occurs because many small

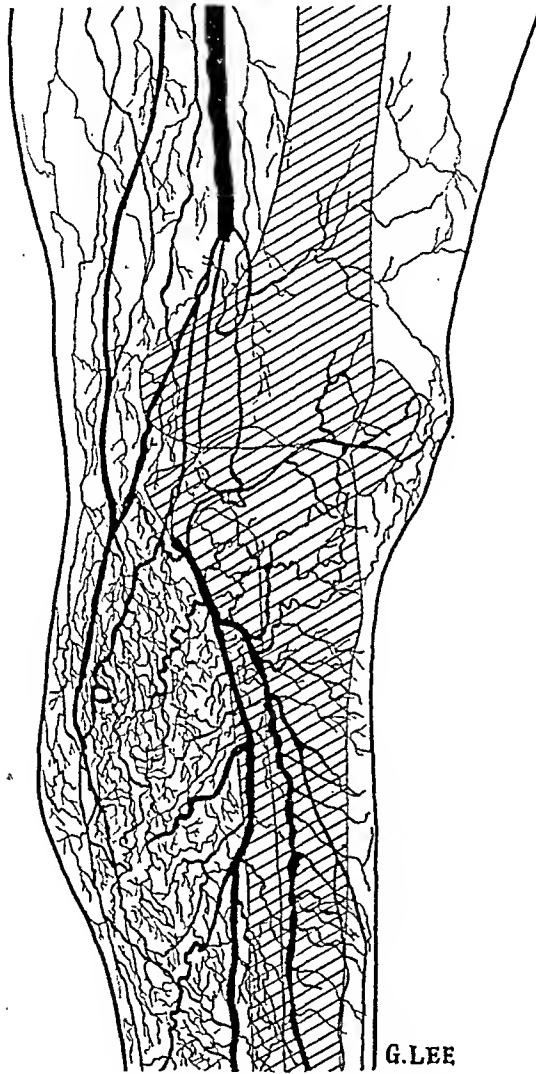


Fig. 3.—Case of gangrene of the toes, with complete obliteration of the popliteal artery. Intermittent claudication is not a symptom, presumably because the development of small muscular branches (which note) has resulted in a sufficient volume of blood to the muscles.

vessels are called into play by the exercise. It may therefore be assumed that patients with intermittent claudication react to exercise as do normal individuals, though to a more limited degree.

It is the abnormal distribution of the blood supply and the inaccessibility of certain portions of the muscles which produce impaired nutrition. There seems no reasonable doubt that the vascular changes which we have outlined impair the nutrition of muscle fibers. There is always, as

we have pointed out, a diminution in the volume flow of blood to the various muscles, and there are areas of muscle fiber in which the arterial supply is completely obliterated. These fibers, however, although deprived of their immediate arterial supply, do not die promptly, as would be expected, since they receive nutrition through the tissue spaces from the venous circulation.

Tissue cells, it must be remembered, do not come directly into contact with the arterial or venous blood. They receive their nutrition from tissue space fluid or lymph, which is derived from both the arterial and the venous circulation and which, various physiologists<sup>8</sup> have shown, can be altered by obstruction of either of these circulations. Obstruction on the arterial side produces a diminished lymph circulation, while obstruction on the venous side, or increased venous pressure, leads to an increased lymph flow. Nature has provided such a margin of safety between these circulatory systems that slight changes in either produce no pathological results. If there is only a slight change in the arterial flow, there will be a compensatory change in the venous flow to overcome it. An increased arterial flow causes a more rapid venous flow, a slowing or decreased arterial output causes a decrease in the rate of venous flow, so that the venous channels are kept filled.

Normally the volume of arterial blood passing through the capillaries into the venous system is sufficient to keep this system well filled. With exercise there is a tendency to empty the veins with each contraction of the muscles, while with each muscular relaxation the veins are promptly refilled. In arterial obstruction, when there is a lowering of the intraarterial pressure and a marked diminution in the number of functioning small muscular branches, arterioles and capillaries, smaller quantities of blood reach the venous system, which therefore fills more slowly. During exercise the venous system is repeatedly emptied, and when the muscle relaxes there is always some delay before the venules and veins are refilled. During rest the tissue space fluid is adequate for the nutrition of the muscle fibers; during exercise, on the other hand, the venous blood is emptied from the vessels and the tissue space fluid is correspondingly depleted.

The experimental work of Lewis and his co-workers<sup>9</sup> might be quoted in this connection. The theory which they have advanced to explain the pain of intermittent claudication is based upon an elaborate set of experiments dealing with the production of ischemic pain by obstruction of the arterial supply. On the basis of this work they conclude that pain is caused by a product of muscular metabolism, which they term factor P. The background, so to speak, is an inadequate blood supply to the muscles of the parts, the inadequacy being evident only during exercise. When successive muscular contractions occur, the state of the muscle undergoes a progressive alteration, and, as this alteration takes

place, its product, the hypothetical factor P, is given off and collects in the extramuscular tissue spaces. Factor P, which is a physicochemical product, with a cumulative action, is given off during exercise, they believe, even when the blood supply to the muscle is adequate, but under these circumstances it does not rise to the pain level in the tissue spaces. In other words, although obstruction to the blood supply is the essential basis of the pain, the pain stimulus itself, the hypothetical factor P, is a product given off by the muscle fibers.

Lewis' theory is ingenious, but obviously, until factor P has been isolated, it must remain only a theory. It is true, furthermore, that he was dealing with complete obstruction of both the arterial and the venous systems in normal muscles. On the other hand, it cannot be questioned that the pain in such circumstances is similar to the pain of intermittent claudication in arteriosclerosis, and we are inclined to accept his views, except in one respect. In arteriosclerosis, one is dealing with an arterial obstruction and the venous system is presumably patent. During rest the veins supply an adequate amount of lymph to the muscle fibers. During exercise, however, the tissue space fluid is necessarily depleted. This is because, as the result of the lowered blood volume, the veins which empty during the contraction of the muscles in the period of exercise are not promptly refilled during the period of relaxation. As exercise continues and this cycle is constantly repeated, the tissue space fluid becomes more and more depleted. With the depletion of the tissue space fluid, an altered metabolism occurs in the muscle fibers, and an acute starvation, so to speak, exists. The result is that abnormal metabolites, such as the hypothetical factor P of Lewis, are produced, and pain results. As the veins are refilled during rest, the tissue space fluid is replaced, the abnormal metabolites are washed away, the normal cellular metabolism once again takes place, and, as a result, the pain subsides.

#### REFERENCES

1. Lewis, T.: *Vascular Disorders of the Limbs*, New York, 1936, The Macmillan Company.
2. Hermann, L. G.: *Passive Vascular Exercises*, Philadelphia and London, 1936, J. B. Lippincott Company.
3. Veal, J. R., and McFetridge, E. M.: *Vascular Changes in Intermittent Claudication*, *Am. J. M. Sc.* 192: 113, 1936.
4. Brooks, B.: *Pathologic Changes in Muscles as a Result of Disturbances of Circulation*, *Arch. Surg.* 5: 188, 1922.
5. Veal, J. R., and McFetridge, E. M.: *Technical Considerations in Arteriography of Extremities With Thorotrast*, *Am. J. Roentgenol.* 32: 64, 1934.
6. Idem: *Arteriography in Gangrene of Extremities by Use of Thorium Dioxide (Thorotrast): Study Based on Twenty-Seven Cases*, *Ann. Surg.* 101: 766, 1935.
7. Idem: *Adequate Circulation in Extremities; Arteriography as Test for Determining Its Limits; Preliminary Report Based on Thirty Amputations*, *J. A. M. A.* 104: 542, 1935.
8. Starling, E. H.: *Principle of Human Physiology*, Philadelphia, 1930, Lea & Febiger.
9. Lewis, T., et al.: *Observations Upon Muscular Pain in Intermittent Claudication*, *Heart* 5: 359, 1931.

# INTERPRETATION OF ARTERIAL ELASTICITY FROM MEASUREMENTS OF PULSE WAVE VELOCITIES\*

## I. EFFECT OF PRESSURE

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IN THE study of cardiovascular disease a considerable body of knowledge of the physiological behavior of the heart and the small vessels of the periphery has accumulated. The large arteries have, however, received only moderate attention in this regard and yet it is clear from the number of studies devoted to their pathological state that their importance for the circulation is well recognized. The relatively small number of studies concerned with their physiological state is due rather to the lack of accurate and direct methods than to lack of interest. Knowledge of the function of the vascular system as a whole cannot, however, be said to be complete without information as to the behavior of the larger arteries.

Essential hypertension has been rather extensively studied with regard to the action of the heart and the peripheral arterioles. No fact seems clearer than that peripheral resistance is increased in this disease and that this increase is due to constriction of the arterioles.<sup>1, 2, 3</sup> Information as to whether this increase in tone is confined to the muscular coat of the arterioles alone, or whether it extends throughout the musculature of the entire arterial system might then be of assistance in analyzing the mechanisms involved. The chief function of the arterioles is, perhaps, regulation of the flow of blood, and in order to quantitate the function one studies the latter. Similarly, the principal function of the large muscular arteries, aside from the very obvious one of acting as conduits, is dependent upon their ability to stretch, that is, upon their elastic properties. One studies, therefore, their elasticity.

Hypertension was chosen for study because, as just stated, much is known about other parts of the circulatory system and especially because it affords, in the early stages at least, opportunity to study temporary or functional changes in the walls of the arteries. During the progress of this work, valuable information upon this particular point has been published by Haynes, Weiss, and Ellis<sup>4</sup> and by Weiss, Haynes, and Shore.<sup>5</sup> Although the data in the two studies are somewhat similar, differences in mode of analysis and in interpretation of results have made the continuance of work in this laboratory seem important.

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Read before The American Heart Association, Section for the Study of the Peripheral Circulation, at Atlantic City, June 7, 1937.

The method of measuring elasticity of arteries in the intact animal depends upon the close relation which exists between the speed of the pulse wave in, and distensibility of, an artery. The relation was first set forth in detail by Moens in 1878.<sup>6</sup> It is exact but is unfortunately somewhat complex in that a number of factors in addition to the elastic state of the wall affect the speed of transmission. The subject has been recently and thoroughly reviewed in an excellent study of the relation of age to elasticity of the arteries by Hallock,<sup>7</sup> and for this reason only a brief statement concerning the points pertinent to the present subject is necessary. It is plain from Moens' equation (Fig. 1A) that the speed of the arterial pulse wave depends upon at least four variables, one of which is the elastic state of the arterial wall. If other variables could, then, be kept constant or in some way accounted for, an accurate estima-

A

$$v = \sqrt{\frac{g \cdot E a}{\Delta \cdot d}}$$

g = gravity

E = coefficient of elasticity  
of the wall

a = thickness of wall

$\Delta$  = Sp. Gr. of blood

d = diastolic diameter of  
artery

B

3.57

v =

$$\sqrt{\frac{\% \text{ increase in volume per mm. Hg.}}{\text{increase in pressure}}}$$

Fig. 1.—(A) Moens' and (B) Bramwell and Hill's equation relating velocity of propagation of the arterial pulse wave to elastic properties of the arterial wall.

tion of the elasticity of the artery might be made. Unfortunately, this is not the case. Variables must be eliminated or their effects measured by all the means at our disposal, and even then their elimination is only partly successful.

Let us consider these variables successively and discuss what may or may not be done with each.

(1) The specific gravity of the fluid (blood) in the tube varies relatively very little and may, for present purposes, be supplanted by a constant factor.

(2) The diameter of the artery and thickness of its wall cannot, obviously, be measured directly in the intact organism. It is therefore necessary to compare observations made upon the same artery when attempting to evaluate variations in elasticity. Even so, arteries are known to change their diameter and thickness of wall by contracting or

relaxing the muscular coat. It is clear, however, that by changing muscular tone, elasticity is also altered. The observed change in velocity of propagation of the pulse wave is due partly to change in size of the artery and partly to change in elasticity. Bramwell and Hill<sup>2</sup> in 1922, recognizing this fact, transformed Moens' formula so that it involved only speed of the pulse wave and pressure within the artery (Fig. 1B), permitting calculation of the pressure-volume curve for any given speed in a particular artery. They showed clearly that error due to thickness of wall and diameter was, in any one artery, small. It must be borne in mind however that the equation does not distinguish between the part played by the thickness of the wall and the diameter of the artery from that part played by the constitution of the wall. The curves obtained in this way are simply a measure of the sum of these effects upon the elasticity of the artery and not necessarily of the elastic state of the walls alone. Change in speed of the pulse wave due to change in state of the arterial wall and change in caliber of the artery seem, still, to be inseparable.

(3) Perhaps most important of all the variables which relate speed of pulse wave to elasticity is the pressure within the artery. It is important not only because it exerts a great effect upon the speed of the pulse wave but also because its physiological variations are rapid, frequent, and large. Pressure, as such, does not appear in Moens' formula but is of course implicit in the elastic coefficient  $E$  which is a ratio of volume to pressure. All observers agree, however, that change in pressure is not proportional to change in volume in such a way as to agree with Hook's law. The coefficient of elasticity is therefore not a constant—it is a variable dependent, for one thing, upon pressure.

Some notion of the magnitude of the effect of pressure upon the distensibility of the arterial wall may be obtained by considering a curve of increase in volume for successive increments of pressure (Fig. 2) derived from a curve relating speed to pressure in an excised artery. It is plain that much greater force is required to obtain the same degree of distention at high than at low pressures. It is, consequently, necessary to know at what pressure the elasticity of the artery is being measured before drawing conclusions concerning the state of the wall.

When velocity is used as an index of distensibility the pressure at which it is measured is, then, important. The problem becomes, in the intact animal, which pressure is important—systolic, diastolic, or mean? Obviously it is the pressure at which the pulse wave is transmitted and this is, in intact animals, diastolic pressure, since velocity of the pulse wave is customarily calculated by measurements made upon the first upstroke of the pulse wave, i.e., the one which begins at the diastolic level of pressure. Wiggers<sup>3</sup> has shown that the pressure waves produced at systolic level travel at much higher speeds than those ordinarily

recorded for pulse wave transmission. Frank<sup>10</sup> has demonstrated that reflected waves do not appear upon the pulse wave soon enough to disturb the initial upstroke beginning at diastolic levels of pressure at least as far as the radial and femoral pulse is concerned. In spite of the fact that logic compels acceptance of the dependence of velocity of the pulse wave upon diastolic pressure, many workers continue to attempt to relate the velocity of the pulse wave to systolic pressure, mean pressure, and pulse pressure. And if one keeps clearly in mind that speed can have only an indirect relationship with these levels of pressure the procedure may well be useful.

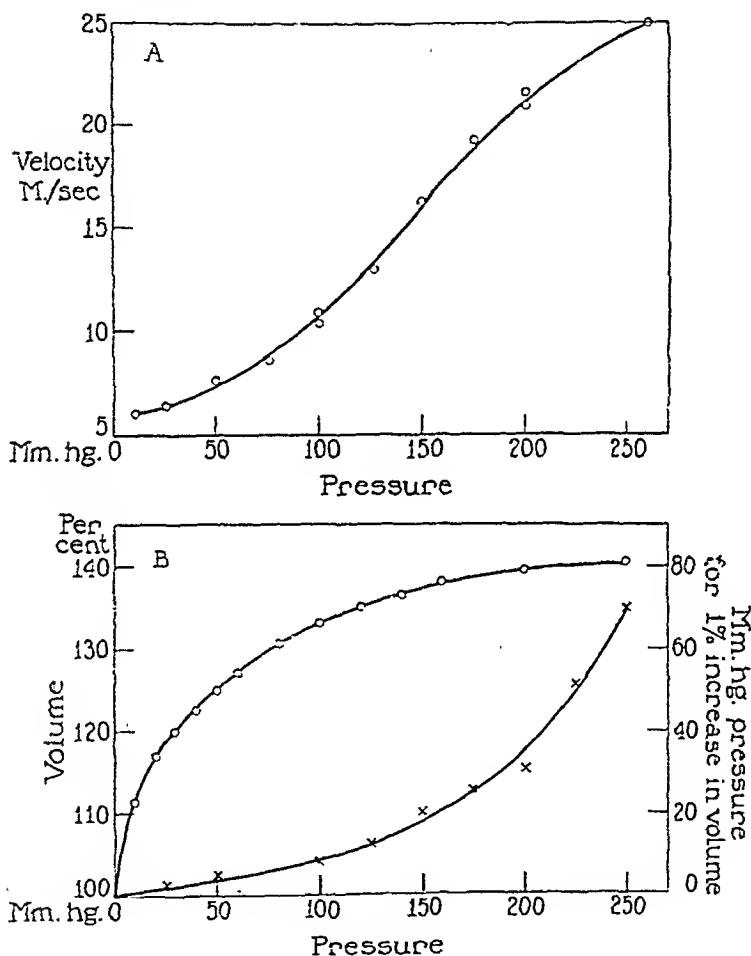


Fig. 2.—(A) A curve of the relation found to exist between speed of transmission of the pulse wave along, and pressure within, the normal brachial artery excised from the arm of a man aged forty years, eighteen hours after death. (B) The curve joining the points marked  $\times$  is calculated from the equation of Bramwell and Hill and shows the increase with pressure of the force required to produce a given increase in volume; the one joining the circles illustrates the progressively declining increase in volume for each successive increase in pressure.

But the usual reason for correlating the pulse wave velocity with various pressure levels appears to be that in dealing with large groups of individuals most authors<sup>11-15</sup> have been unable to find correlation with the diastolic level. The reason for this will be made clear in a few moments. First it seems advantageous to describe several experiments in intact dogs designed to alter systolic without altering diastolic pressure, and the reverse, in order to test separately their effect upon



velocity of the pulse wave. This step seems necessary because as Weiss and collaborators also have pointed out confusion exists in medical literature as to which level of pressure is the important one.

The method of Bramwell and Hill<sup>8</sup> employing two hot wire sphygmographs connected through Wheatstone bridges to two galvanometers and by stiff rubber tubes to two tambours in contact with the iliofemoral artery of dogs (Fig. 3) was used to measure the interval of time between the arrival of the pulse wave at two distant points along the artery. A cannula leading to a Frank manometer was placed in the internal iliac just at its emergence from the iliofemoral artery. Three methods were employed for changing one level of pressure without the other: First, partially clamping the aorta just above the proximal tambour was found within certain limits to reduce systolic without altering, significantly, diastolic pressure; second, an arteriovenous shunt through artificial peripheral resistance just beyond the distal tambour allowed some variation of diastolic without noteworthy change in systolic pressure. Two examples will suffice to illustrate their use. The first (Fig. 4) illustrates not only the effect of clamping the aorta but also the constancy of the preparation in the absence of any meddling. The four parts of the record were obtained during a period of thirty minutes. When the aorta was severely clamped (*C*) the systolic pressure dropped sharply without materially affecting the pulse wave velocity or the diastolic pressure. Otherwise the record is quite constant. Combinations of both methods are shown in the second example. In *A* (Fig. 5) the aortic clamp is in place, wide open, the arteriovenous shunt closed, in *B* the aorta has been compressed to roughly one-third or one-half the cross section. Systolic pressure has fallen sharply, neither diastolic pressure nor the velocity of the pulse wave has changed significantly and do not change with removal of the clamp and consequent return of systolic pressure to its previous level. When, with aortic clamp open, the artificial arteriovenous aneurysm or shunt is opened, the diastolic pressure in the artery falls 20 mm. Hg, and the pulse wave velocity decreases from 10.7 to 8.5 M./sec., whereas the systolic level is not materially affected. Now when the aortic clamp is again applied (*D* and *E*) systolic pressure falls rapidly while diastolic pressure and velocity of the pulse wave both increase slightly. With release of the aortic clamp (*F*) the systolic pressure returns to its former level but not until the arteriovenous shunt is closed (*G*) do diastolic pressure and pulse wave velocity follow suit.

The third procedure employed for changing one level of pressure without the other was to cut the leaflets of the aortic valve by thrusting a barbed hook sheathed in a long cannula until its arrival at the valve down the left carotid artery through the valve and withdrawing it. An enormous fall in diastolic pressure can in this way be induced without any drop, in fact with a rise, in systolic pressure. Velocity of the pulse wave

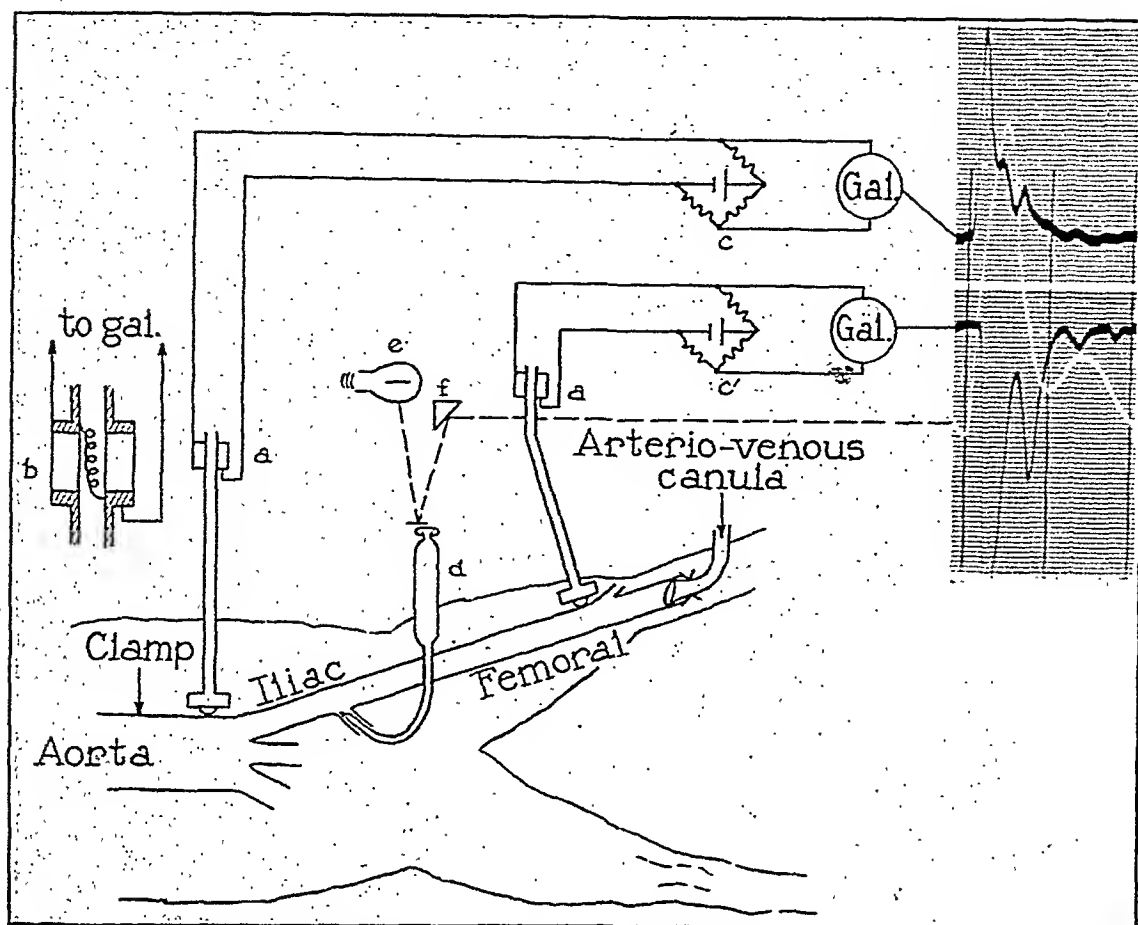


Fig. 3.—A diagram is shown of the arrangement of apparatus for obtaining simultaneous records of pressure within and speed of transmission of the pulse wave along the iliofemoral artery of dogs. *a, a*, hot wire sphygmographs; *b*, sphygmograph enlarged; *c, c*, Wheatstone bridges; *d*, Frank capsule and cannula in the internal iliac artery; *e*, source of light; *f*, prism.

The inset in the right hand upper corner is a reproduction of an actual record. In this figure and in Figs. 4, 5, and 6, the black curves are written by the two galvanometers, and from the difference in time between the upstroke of one and the downstroke of the other the velocity of the pulse wave is calculated. The curve written in white is the record of pressure obtained by the Frank capsule.

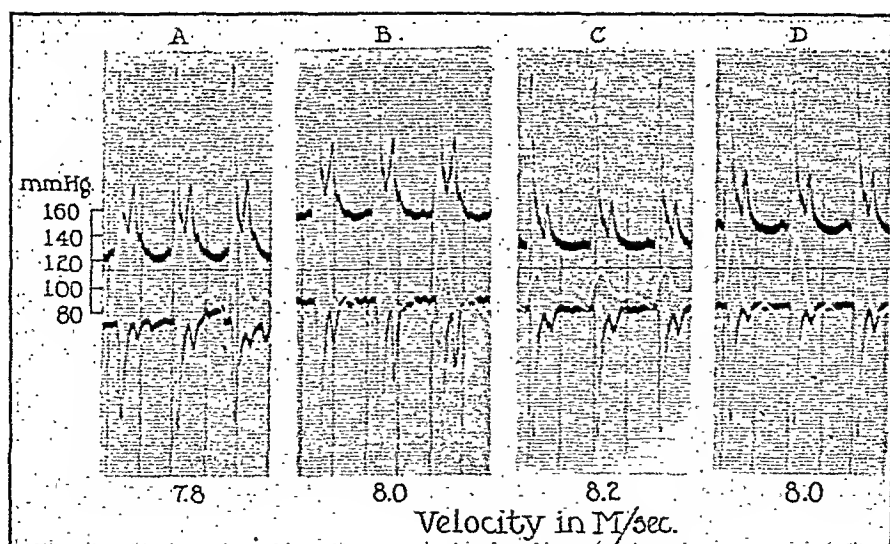


Fig. 4.—Simultaneous records of pulse wave velocity and pressure obtained from the iliofemoral artery of a dog are shown. *A, B*, and *D* before and after, and *C* during application of an aortic clamp.

parallels closely the changes in diastolic pressure without relation to either systolic or mean pressure. A single example is given (Fig. 6). Before cutting the valve, the systolic level was during a fifteen minute period (A) about 158, the diastolic approximately 118. The velocity of the pulse wave varied from 7.7 to 8.0 M./sec. (A). One cusp was then completely cut through and a small hole torn in another (as shown by

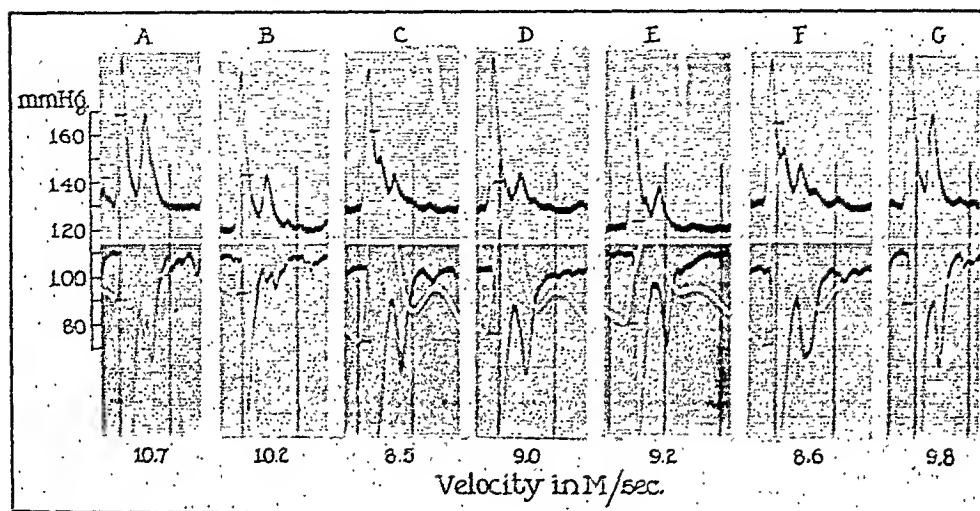


Fig. 5.—Simultaneous records of pulse wave velocity and pressure obtained from the iliofemoral artery of a dog are shown. A with aortic clamp and arteriovenous shunt in place, clamp open, shunt closed; B with the aorta partially clamped, shunt still closed; C, D, E, and F arteriovenous shunt open, C and F aortic clamp open, D and E two stages in the closure of the aortic clamp; G as in A.

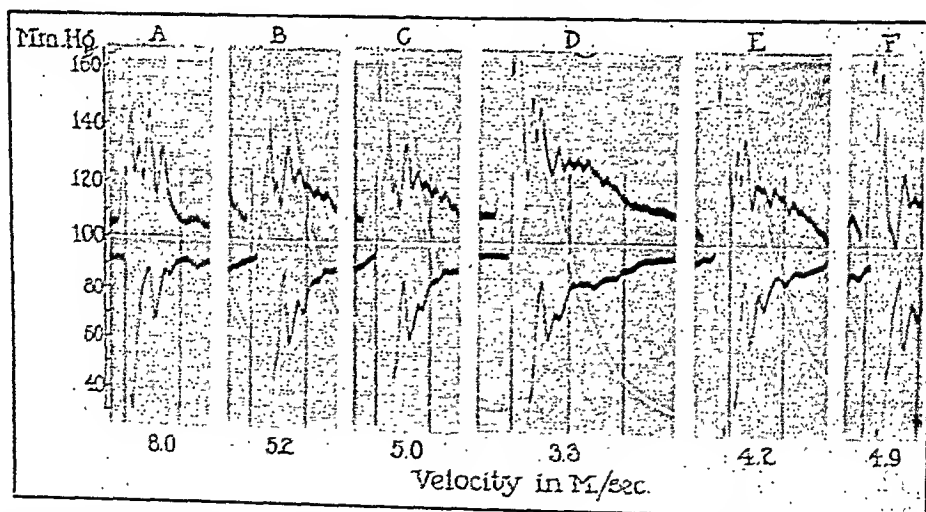


Fig. 6.—Simultaneous records of pulse wave velocity and pressure obtained from the iliofemoral artery of a dog are shown. A control; B and C after cutting aortic valve; D after slowing by vagal stimulation; E partial recovery from vagal stimulation at a time when systolic level has returned to its original level (compare A); F complete recovery from stimulation, i.e., similar to E.

subsequent examination of the heart). Systolic level rose slightly, diastolic pressure fell abruptly and with it velocity of the pulse wave (B and C). When in addition the vagus was stimulated to slow the rate, diastolic pressure and pulse wave velocity both fell much farther. Dur-

ing this period there was also a drop in systolic pressure (*D*) but a record taken during recovery from stimulation (*E*) secures a point in time when systolic pressure has reached the original level while diastolic pressure and velocity remain at one-half their original values. Plainly velocity follows the diastolic level. In the last record (*F*), the state immediately after section of the valve has again been reached.

These observations strongly reinforce the logical argument that velocity of the arterial pulse wave depends, so far as it depends on pressure at all, unequivocally upon diastolic level.

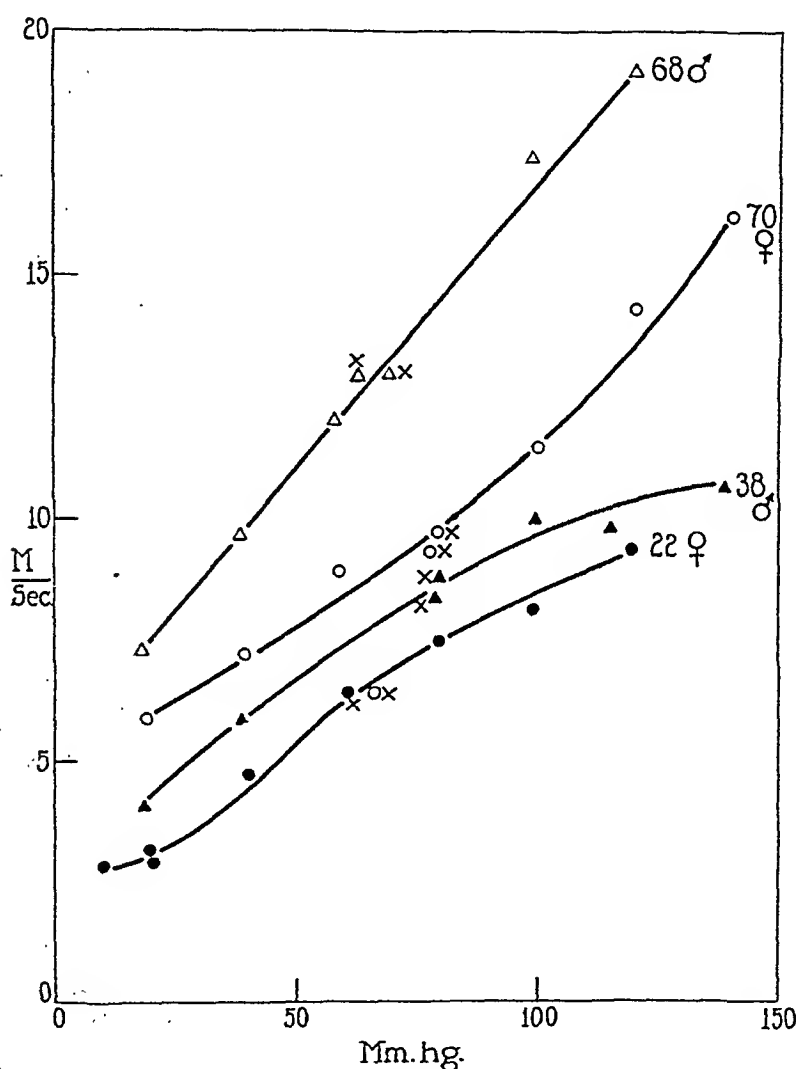


Fig. 7.—Curves describing the relation of pulse wave velocity to diastolic pressure obtained in the brachioradial arteries of four normal individuals are shown to illustrate variability among individuals. The observations obtained at the naturally existing pressures are marked by X.

With the knowledge that speed of pulse wave varies with diastolic pressure in accordance with prescribed laws, the effect of pressure upon the speed of the pulse wave in the brachioradial artery in normal individuals and in individuals suffering from hypertension was studied. If diastolic pressure is the one upon which the speed of the pulse depends, the methods of Bramwell, McDowall, and McSwiney<sup>16</sup> and Hem-

ingway, McSwiney, and Allison<sup>17</sup> for altering the *effective* pressure within an artery can be considered as altering essentially diastolic pressure. The method consists in measuring the speed of the pulse wave while a known portion of the arm between the two points selected for recording the arrival of the pulse waves is subjected to various external pressures. From these measurements the speed of the wave at various diastolic pressures in the region so treated can be calculated and pressure-speed curves constructed for each subject.

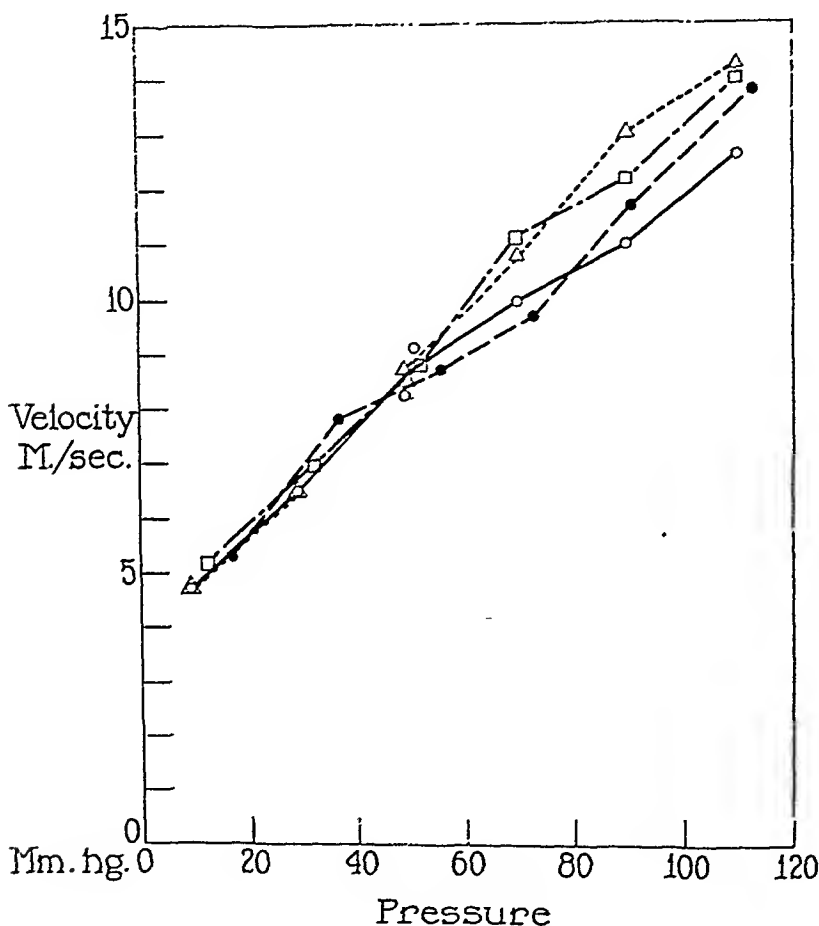


Fig. 8.—Four curves are shown relating pulse wave velocity and diastolic pressure obtained from one individual at intervals during a period of six months to illustrate individual constancy.

From such curves (Fig. 7) the velocity of pulse wave at any pressure may be calculated by reading off the velocity recorded at the intersection of the curve with the ordinate representing the desired pressure. That individual curves are necessary for calculating the velocity of each subject at a particular pressure is to be expected from the great differences between individual relationships noted by Hemingway, McSwiney, and Allison<sup>17</sup> and found also in the present series. Four are shown as examples (Fig. 7).

The velocity of the brachioradial pulse wave was measured in 48 normal individuals whose ages varied from thirteen to ninety-one years at the natural diastolic pressure and then a curve of the pressure speed relations was constructed for each individual in the manner just described. In 20 subjects from two to five curves were constructed for each. In contrast to the great differences between individuals the curve of a particular individual varies but little from week to week (Fig. 8). The velocity at 80 mm. mercury was then calculated for each individual. When the whole group of velocities naturally observed is plotted against age it is readily seen that speed of the pulse wave increases with age as has been repeatedly shown. And if the velocities are calculated at 80

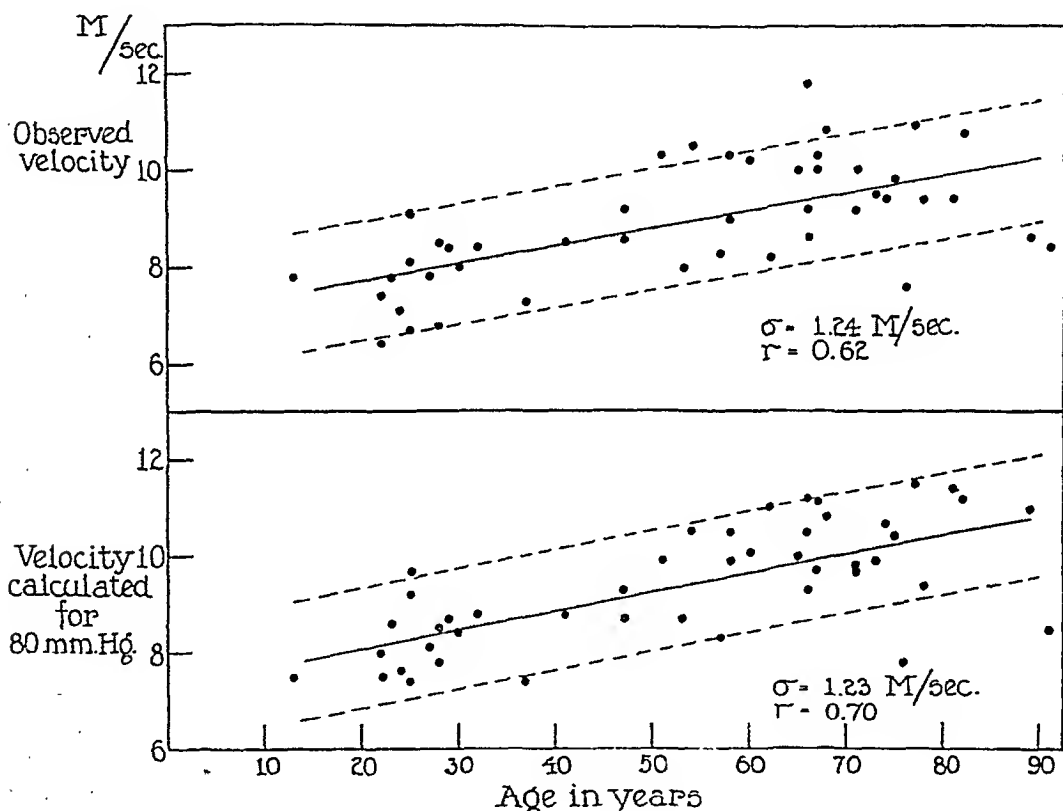


Fig. 9.—Velocities of the pulse wave in the brachioradial arteries of forty-eight normal individuals are plotted against age; above are the velocities obtained at natural diastolic pressures, below are those calculated in the manner described in the text at 80 mm. Hg. In this figure and in Fig. 10, the solid lines represent the regression equations, the dotted ones, the standard error of estimate.

mm. Hg and plotted in the same way, it becomes plain that adjusting them for diastolic pressure has not had an observable effect (Fig. 9). The standard deviation is one and a quarter meters and correlation with age is highly significant in either case (0.62 and 0.70). Correlation with diastolic pressure is not significant just as most workers have found. The reason for lack of significant correlation is probably due to the fact that the observed range of variation in diastolic pressures in normal people is plainly too small to bring out correlation with velocity in the presence of the much larger variations in velocity found to occur from one

individual to the next. The standard deviation of diastolic pressure is 10.2 mm. Hg. A change of 10.2 mm. Hg in the average individual would change the velocity of the pulse wave roughly only 0.4 and 0.6 of a meter or one-third the standard deviation of the velocity of the pulse wave at a given age.

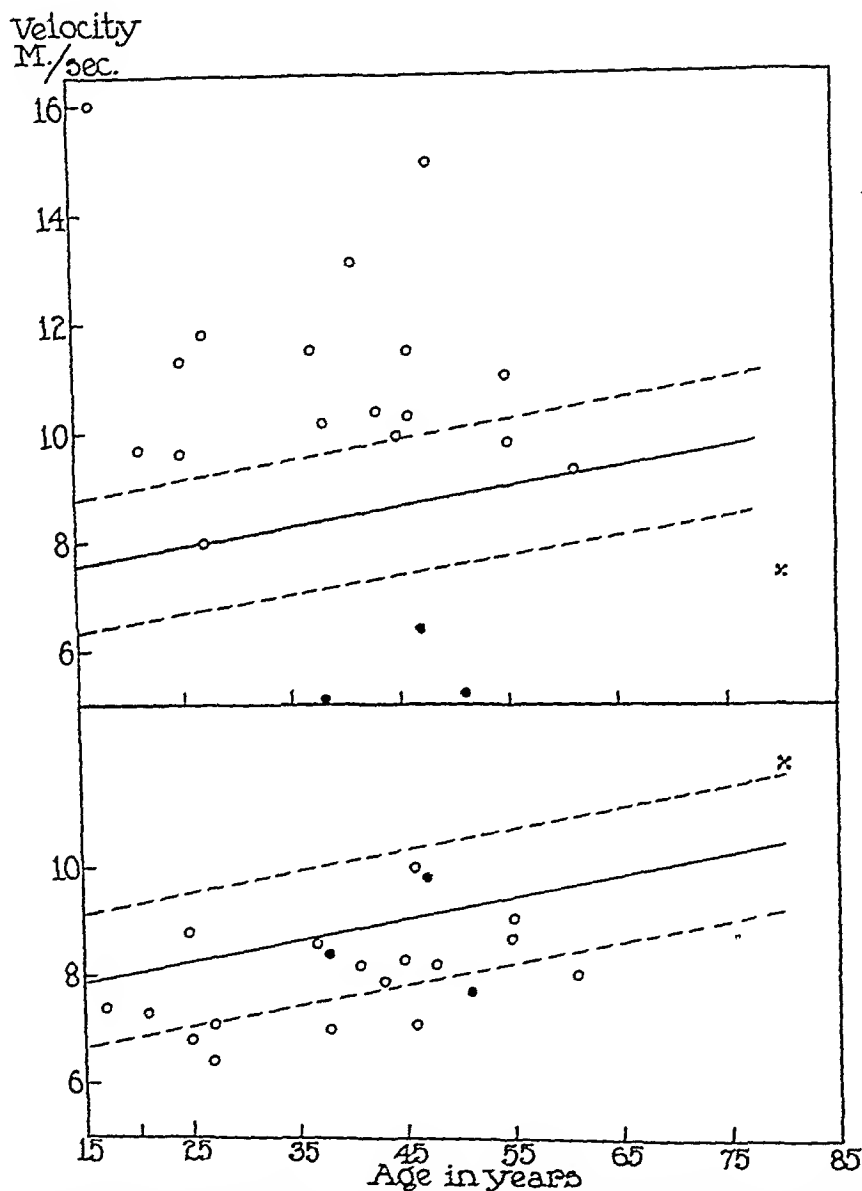


Fig. 10.—The velocities of the pulse wave in the brachioradial arteries of seventeen individuals with arterial hypertension (open circles) and of three with aortic insufficiency (closed circles) are shown according to age; above at natural diastolic pressures; below, calculated at 80 mm. Hg.

When one turns now to individuals with hypertension in whom the level of diastolic pressure is far different from normal, the effect of pressure on the velocity of the pulse wave becomes clear because it is great. The naturally recorded velocities in 18 patients in whom there was no

evidence of arteriosclerosis, were very high (from 8 to 16 M./sec.) (Fig. 10 upper). When their velocities are calculated at 80 mm. Hg they come to lie at, or even below, normal ones (Fig. 10 lower). Conversely, the velocities of normal arteries, calculated at 130 mm. Hg are as high as hypertensive ones. There is, then, no reason to believe that the distensibility of the larger arteries in patients suffering from hypertension differs from the normal except perhaps as an after effect of stretching, a phenomenon of considerable interest and one about which more will be said at another time. It can from these observations be inferred that the tone of their muscular coats is probably not greater than that of normal subjects. There are exhibited also three cases suffering from aortic insufficiency (closed circles Fig. 10) whose diastolic pressures ranged from 20 to 40 mm. Hg. They too have normal rates of transmission of the pulse wave at 80 mm. Hg.

#### COMMENT

If the speed of the arterial pulse wave is dependent upon the level of diastolic pressure, so far as it is dependent upon pressure at all, explanation of the close relation between speed of pulse wave and pulse pressure observed by Haynes, Ellis, and Weiss<sup>4</sup> becomes necessary. This relationship can be only indirect and the presence of other variables affecting both speed of the pulse wave and pulse pressure is, at once, suggested. In the several distinct groups of individuals from which the data were obtained—normal, hypertensive, arteriosclerotic, combinations of the two latter groups and a few individuals suffering from aortic insufficiency—certain factors which should affect both speed of pulse wave and pulse pressure would seem to be present.

First in hypertension the high diastolic pressure is the factor upon which both the high pulse pressures and high velocities of the pulse wave depend. For it has just been shown that speed of pulse wave increases with diastolic pressure. It is well-known that at high pressures a greater change in pressure is needed for the same change in volume than is necessary at low pressures.<sup>18</sup> Since there is considerable evidence that change in volume i.e., cardiac output and blood flow, is the same in hypertensive as in normal individuals<sup>5, 19, 20, 21</sup> the pulse pressure would, of necessity, be increased.

Secondly, in arteriosclerosis, the rigidity of the arterial wall is the factor upon which both the high pulse pressure and the high pulse wave velocity depend.

Thirdly, those individuals whose large pulse pressure is due to aortic insufficiency, and in whom there is no increase in rigidity of the arterial wall either from simple stretching (increase in diastolic pressure) or from changes in the constitution of the wall, exhibit a marked contrast to the two former groups. The large pulse pressure is not accompanied by a high velocity of the pulse wave. The velocities are, on the contrary,



rather low as are also the diastolic pressures. In short, velocity of propagation of the arterial pulse wave is not directly related to pulse pressure. Association of these phenomena is due to the presence of some third factor, in the present instances, marked stretching of, or change in structure of, the arterial wall upon which, on the one side pulse pressure, and on the other side velocity of the pulse wave, depends.

#### SUMMARY

1. It is well known that a considerable portion of the variation in arterial pulse wave velocity as measured in living individuals is due to size and thickness of wall, and to pressure within the walls, as well as to actual changes in elasticity of the wall itself. When an index of the elasticity of the arterial wall is sought by measuring pulse wave velocity, the error due to size and thickness of the wall can in part be taken into account only by measurements carried out upon the same artery; that due to pressure can be largely accounted for by individual relationships found to exist between speed of the pulse wave and pressure.

2. The pressure upon which the speed is dependent is not systolic, mean or pulse pressure but unequivocally diastolic pressure. The logical argument for this conclusion is supported by studies of pulse wave velocity carried out in dogs in which the levels of systolic and diastolic pressures were varied independently. The velocity of the pulse wave was not affected by variations in systolic pressure alone and hence neither by mean or pulse pressure. Changes in diastolic pressure only were regularly accompanied by changes in pulse wave velocity.

3. When the effect of the higher diastolic pressures occurring in hypertensive individuals without obvious arteriosclerosis is taken into account, it seems that the elastic properties and, inferentially, the tone of the muscular coats, of the larger arteries behave like those of normal ones.

ADDENDUM.—Since the above article was written, M. Prinzmetal and E. T. Oppenheimer have published observations upon patients with hypertension (*Rôle of Arteries in Peripheral Resistance of Hypertension*, *Proc. Soc. Exper. Biol. & Med.* 36: 675, 1937) which strengthen the point of view just presented by furnishing evidence of an altogether different nature that arteries larger than the digital arteries are not necessarily involved in producing hypertension.

#### REFERENCES

1. Weiss, S., and Ellis, L. B.: The Quantitative Aspects and Dynamics of the Circulatory Mechanism in Arterial Hypertension, *AM. HEART J.* 5: 448, 1930.
2. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension With Special Reference to the Vasomotor System, *J. Clin. Investigation* 15: 63, 1936.
3. Pickering, G. W.: The Peripheral Resistance in Persistent Arterial Hypertension, *Clin. Sc.* 2: 209, 1935-36.
4. Haynes, F. W., Ellis, L. B., and Weiss, S.: Pulse Wave Velocity and Arterial Elasticity in Arterial Hypertension, Arteriosclerosis and Related Conditions, *AM. HEART J.* 11: 385, 1936.
5. Weiss, S., Haynes, F. W., and Shore, R.: The Relation of Arterial Pulse Pressure to the Hemodynamics of Arterial Hypertension, *AM. HEART J.* 11: 402, 1936.
6. Moens, A. L.: *Die Pulscurve*, Leiden, Brill, 1878.

7. Hallock, P.: Arterial Elasticity in Man in Relation to Age as Evaluated by the Pulse Wave Velocity Method, *Arch. Int. Med.* 54: 770, 1934.
8. Bramwell, J. C., and Hill, A. V.: The Velocity of the Pulse Wave in Man, *Proc. Roy. Soc. ser. B.* 93: 298, 1922.
9. Wiggers, C. J.: *Physiology in Health and Disease*, Philadelphia, 1934, Lea and Febiger.
10. Frank, O.: Die Theorie der Pulswellen, *Ztschr. f. Biol.* 85: 91, 1926.
11. Sands, J.: Studies in Pulse Wave Velocity. III. Pulse Wave Velocity in Pathological Conditions, *Am. J. Physiol.* 71: 519, 1924.
12. Turner, R. H., and Herrmann, G. R.: Pulse Wave Velocity Under Varying Conditions in Normal and Abnormal Human Cardiovascular Systems, *J. Clin. Investigation* 4: 430, 1927.
13. Bazett, H. C., and Dreyer, N. B.: Measurements of Pulse Wave Velocity, *Am. J. Physiol.* 63: 94, 1922.
14. Eismayer, G., and Saeger, W.: Die Pulswellengeschwindigkeit in verschiedenen Gefäßgebieten; die Pulswellengeschwindigkeit in verschiedenen Gefäßbieten bei Kreislaufgesunden im Ruhezustand und unter Einwirkung von Medikamenten, *Ztschr. f. d. ges. exper. Med.* 96: 233, 1935.
15. Wezler, K.: Abhängigkeit der Arterienelastizität vom Alter und dem Zustand der Wandmuskulatur, *Ztschr. f. Kreislaufforsch.* 27: 271, 1935.
16. Bramwell, J. C., McDowall, R. J. S., and McSwiney, B. A.: The Variation of Arterial Elasticity With Blood Pressure in Man, *Proc. Roy. Soc. ser. B.* 94: 450, 1923.
17. Hemingway, A., McSwiney, B. A., and Allison, P. R.: The Extensibility of Human Arteries, *Quart. J. Med.* 21: 489, 1928.
18. Fahr, G.: Work of the Left Ventricle in Normal Hypertension and Arteriosclerosis, *Proc. Soc. Exper. Biol. & Med.* 24: 405, 1927.
19. Gladstone, S. A.: Cardiac Output and Arterial Hypertension. 1935. A partial report of the investigations conducted at Mt. Sinai Hospital, New York City.
20. Starr, I., Collins, L. H., and Wood, F. C.: Studies of the Basal Work and Output of the Heart in Clinical Conditions, *J. Clin. Investigation* 12: 13, 1933.
21. Holman, D. V.: Cardiac Output in Essential Hypertension. Observations of the Effect of Sympathectomy. (To be published.)

# Department of Clinical Reports

## SIMULTANEOUS QUADRILATERAL ACUTE ULCERATIONS IN THROMBO-ANGIITIS OBLITERANS: REPORT OF A CASE\*

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NEW YORK, N. Y.

IN THE years since von Winiwarter<sup>1</sup> first separated the syndrome which we now call thrombo-angiitis obliterans from the welter of ill-defined diseases of the circulation, physicians have learned to diagnose and treat the condition with increasing ease and accuracy. This report is deemed worthy of presentation because we have been unable to find any evidence, either by a search through the literature or by inquiry from the heads of a number of the largest vascular clinics in the country, of a previous patient with thrombo-angiitis obliterans who exhibited simultaneous acute quadrilateral ulcerations. The history and management of the patient also illustrate some specific problems in the diagnosis, treatment, and prognosis of the disease.

### CASE REPORT

J. K., a thirty-nine-year-old American bus chauffeur of Aryan stock, was seen in the Vascular Clinic of the New York Post-Graduate Hospital on Feb. 23, 1937. He was admitted to the hospital on the same day.

His complaints dated back two and one-half years, when an ulcer developed on the tip of the right fourth finger. After several days of progression it was curetted down to the bone, and the wound healed slowly in a few weeks. Subsequently ulcers appeared on the third finger of the right hand, the fifth finger of the left hand, the second, third, and fourth toes and heel of the right foot, and the fourth toe of the left foot. A few had healed, but at the time of admission at least one lesion was present on each extremity, to be described below.

Treatment had previously consisted of diathermy, injections of unknown composition, and fever therapy in a hyperpyrexia apparatus, all without satisfactory response. About two months before admission, while in the midst of the hyperpyrexia treatment, a lesion which developed into an ulcer appeared on the left fourth toe, and with it severe rest pain occurred which was worse at night. Six weeks later cramp-like pains in the left calf were noticed, and at the time he was seen in the clinic the patient could barely walk because of this pain (whether this was true claudication or muscle strain, due to favoring the foot because of the open ulcer, could not be definitely determined).

There was no previous history of phlebitis, frostbite, or major illnesses or operations. He had smoked an average of 20 popular-brand cigarettes daily for years; ingestion of rye bread was rare. His weight had decreased 25 pounds in two years.

The general physical examination revealed no significant findings other than those noted below. Blood pressure averaged 106/78. The nails of all fingers were striated and brittle. The right fourth finger was about 0.5 cm. shorter than the corresponding finger on the left hand and the nail was curved down over the tip. This shortening had been produced by a previous ulcer, as above noted. All fingers showed chronic

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rubor, especially the second and fifth on the left hand. There was a fluctuant discolored gangrenous area at the tip of the right third finger, and discoloration of the bed of the thumbnail. The left fifth finger was noticeably cooler than the other

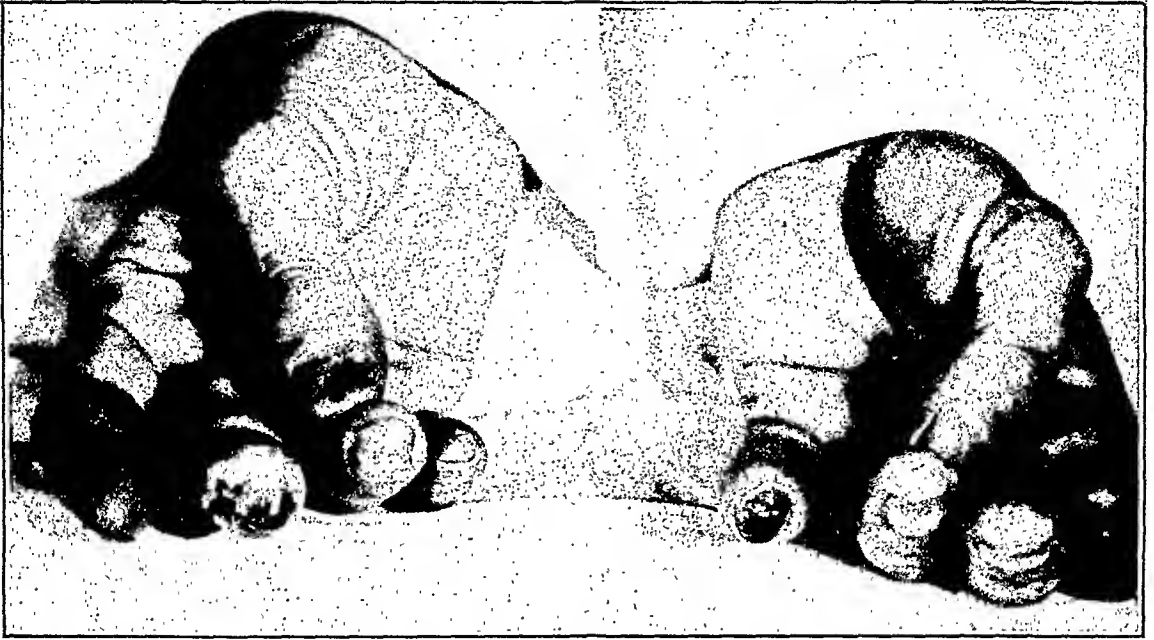


Fig. 1.—Appearance of hands on admission. Note ulcer on right third finger, down curving nail on right fourth finger, discolored nail bed of right first finger, ulcer on left fifth finger.

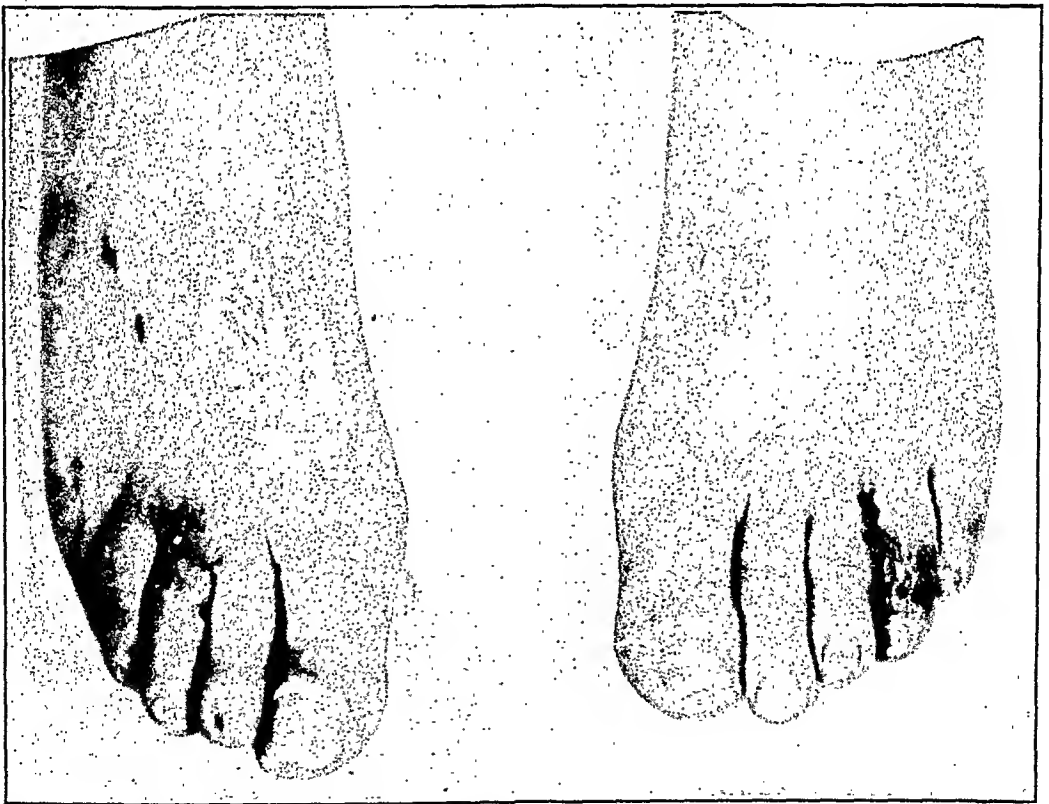


Fig. 2.—Appearance of feet on admission. Note ulcers of right third toe and left fourth toe. A large ulcer of the right heel does not show.

fingers, and at its tip was a black, sloughing and crusted ulcer from which pus in small amounts could be expressed. The Allen test<sup>2</sup> revealed defective filling of the left ulnar artery. The other major arteries of the upper extremities were smooth and strongly pulsatile (Fig. 1).



Fig. 3A.

Fig. 3. A and B.—Arteriograms of left and right hands. The digital arteries supplying the fifth finger of the left hand and practically all of the fingers of the right hand are not well visualized. The arteries proximal to the wrist are not involved.

The dorsum of the left foot was noticeably swollen. All toes showed rubor on dependence, especially the third and fifth on the right and the second and fifth on the left. On elevation all toes and the left foot blanched almost dead-white. On



Fig. 3B.

(See legend on opposite page.)

the medial aspect of the right third toe was a large irregular area of gangrene; on the heel was a shallow irregular ulcer 1.5 cm. in diameter. An irregular necrotic area was present on the dorsal aspect of the left fourth toe. Both feet were cool.

The major vessels of the lower extremities were strongly pulsatile except the right dorsalis pedis, which was feeble, and the left dorsalis pedis, which was absent. After edema had subsided there were times when this could be made out faintly (Fig. 2).

Oscillometric examination of the extremities yielded adequate readings at all levels except the feet, where small but definite deviations of the needle could be seen. Immersion of both upper extremities in water baths maintained at 42 to 46° C. (107.5 to 115° F.) for over forty minutes<sup>3</sup> failed to produce a rise in temperature in the toes, although there was a generalized vasodilatation. Tests with tobacco extracts for skin sensitivity, performed by Dr. F. H. Westcott of our clinic, were negative. Blood, serological, and urine examinations were negative. Blood cholesterol was 165 mg. per 100 c.c.

Arteriographic studies of the upper extremities with a contrast medium of thorium dioxide sol were performed, with the following findings (Fig. 3): in the right

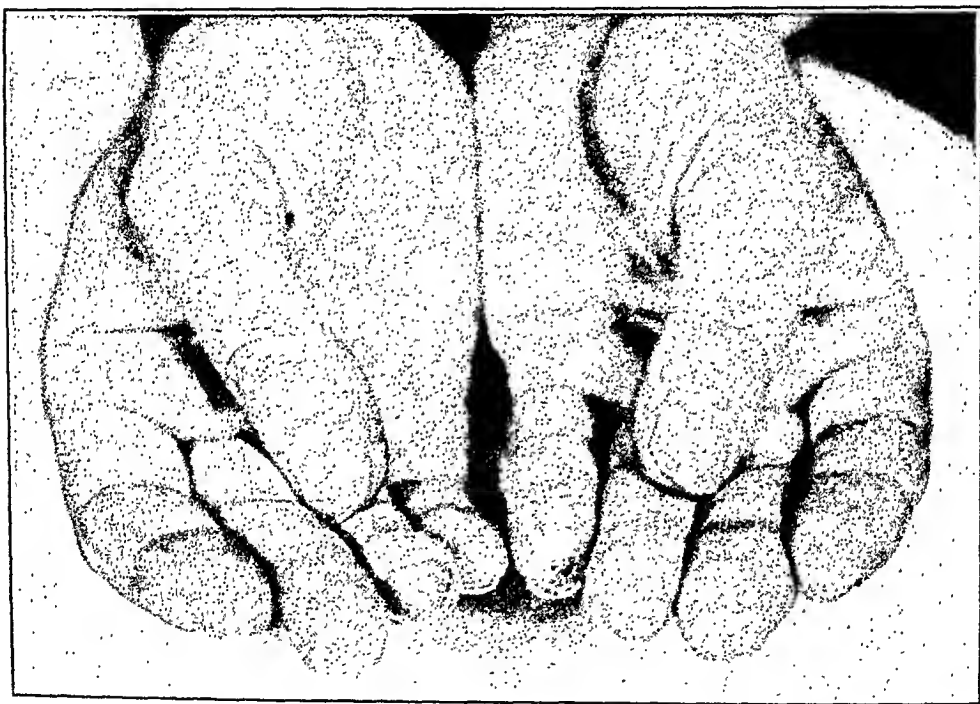


Fig. 4.—Appearance of hands on discharge, seven weeks later.

upper extremity, the major vessels were well visualized down to the fingers. There was some degree of obliteration of practically all of the digital vessels, with occlusion most marked in the fourth finger. In addition there was trophic absorption of the terminal tuft of the ring finger, and similar, less marked changes in the middle and little fingers. In the left upper extremity all of the major vessels visualized well down to the fingers. There was obliteration of vessels supplying the fifth finger, and some obliteration of the arteries of the second and fourth fingers. Increased radiotransparency of the terminal phalanx of the fifth finger was observed. The changes as seen in Fig. 3 are typically those found in thrombo-angiitis obliterans. Unfortunately attempts at arteriographic studies of the lower extremities were unsuccessful.

*Treatment.*—Complete abstinence from tobacco was enforced. The patient was kept in bed, with the lower extremities continuously covered with a cradle and with a thermostatically controlled heating unit\* which kept the temperature within the

\*Cradle and thermostatically controlled heating unit furnished through the kindness of Valverde Laboratories, New York.

cradle at 33 to 35.5° C. (92 to 96° F.). The hands were immersed in warm borie acid baths for one hour three times daily for a week; at the end of this time the necrotic area at the tip of the left fifth finger could be lifted away, and the fluctuant tip of the right third finger had begun to drain pus. The nails were kept trimmed and small crusts were removed daily. After the first week the hands were soaked twice daily, and finally once daily. For the first few weeks the fingers were bandaged in dry dressings between soaks; thereafter no dressings were used.

The ulcers of the toes and heel were covered with wet dressings of azochloramid in triacetin solution, 1:500. These were kept wet continuously during the day. The skin of both lower extremities was kept soft with lanolin.

In addition to these local measures the patient was given typhoid vaccine\* intravenously, beginning with a dose of five million bacilli and increasing each dose

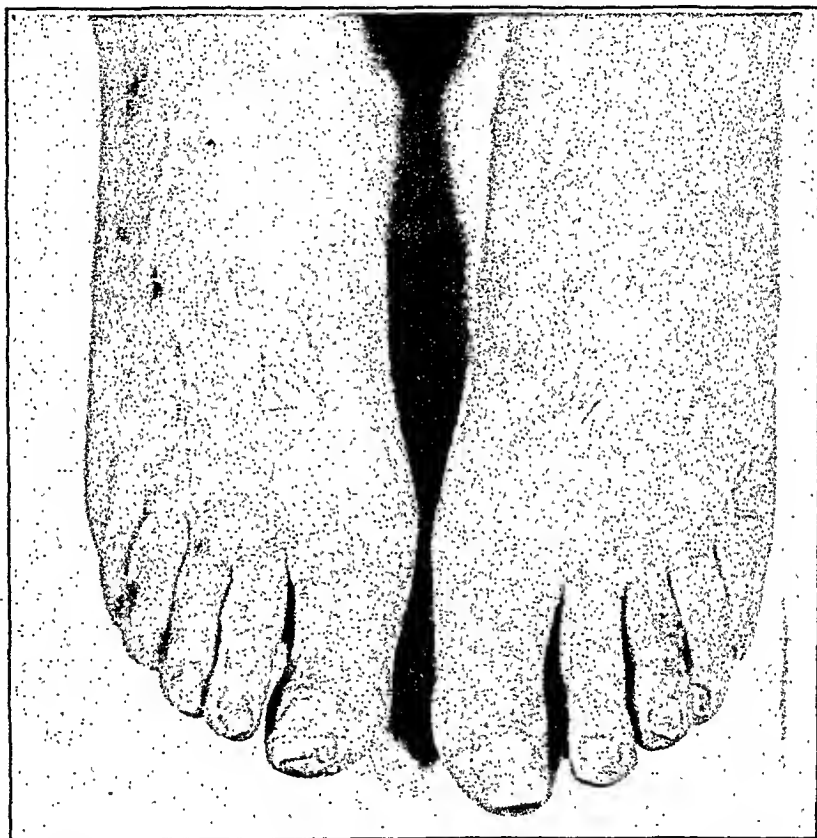


Fig. 5.—Appearance of feet on discharge, seven weeks later.

by five or ten million organisms, depending upon the height of the fever reached with the preceding injection, the object being to obtain about two degrees C. of fever without chill. He received three injections weekly for the first four weeks, and two injections weekly thereafter.

Within a week the ulcer of the right third toe healed, and a few days later the heel covered over. The ulcer of the left fourth toe responded more slowly, but by the end of the second week the purulent discharge had ceased and a dry scab formed, which was slowly lifted off, revealing smooth new epithelium beneath.

The patient was discharged on April 14, 1937, seven weeks after admission. The condition of the extremities at this time is shown in Figs. 4 and 5. All ulcers had healed. The nail of the right third finger had fallen off. This finger continued

\*Typhoid vaccine, 100 million organisms per cubic centimeter. Prepared for intravenous use and supplied through the courtesy of the C. F. Kirk Company, Bloomfield, N. J.



to be cyanosed. A small scab covering the depressed area was the only evidence of the large necrotic ulcer at the tip of the left fifth finger. Five weeks after discharge he was back at work, free from symptoms and without recurrence of open lesions.

#### COMMENT

Thrombo-angiitis obliterans most frequently first attacks the vessels of the feet, but it may appear in the upper extremities alone or in combination with the lower extremities. The disease is, moreover, characteristically remissive and migratory, and open lesions do not usually appear on more than one or two extremities simultaneously. This is the first case in our experience, and in the experience of several large vascular clinics in this country, presenting the typical painful ulcers of the disease on all four extremities at the same time. It is of particular interest also because in spite of the widespread involvement the lesions as determined by arteriographic and oscillometric studies were practically confined to the smaller terminal portions of the vascular tree. Buerger<sup>4</sup> has described a few cases in which there was symptomatic involvement of both upper and both lower limbs and ulcerations in two or three, during the protracted course of the disease. In 1932, Ito and Asami,<sup>5</sup> reporting 27 patients treated by lumbar and sacral ganglionectomy, mention one in whom ulcers appeared serially on the digits of all four extremities over a period of years. This was not uncommon, of course, when the disease was allowed to progress unchecked before the present-day therapy was understood. Starr<sup>6</sup> describes a man who had successive involvement of hands and feet, and who at one time had ulcers on the acral portions of three limbs.

Treatment was completely conservative. As has been definitely demonstrated,<sup>7</sup> abstinence from tobacco is the primary, cardinal principle in the treatment of this disease. We have found azochloramid in triacetin, 1:500, to be a helpful antiseptic wet dressing for use in purulent ulcers of the type described. Fever up to 39° C. (102° F.), without rigor and its accompanying marked vasoconstriction, was attained by the intravenous use of the dilute typhoid vaccine above noted. The height of this nonspecific type of fever was regulated by increasing the dose by five or ten million bacilli with each injection if the preceding treatment had not produced a chill or too severe a febrile reaction. There was relief of the intense pain in the ulcerated areas after the second injection; this is a frequent experience with typhoid vaccine. The use of thermostatically controlled heat as recommended by Starr<sup>8</sup> is extremely important, since overheating of the extremity increases metabolic demands, with resultant increase of pain and spread of gangrene. The temperature should be kept between 33 and 35.5° C. (92 and 96° F.).

Although the ulcers were completely healed at the time of discharge and have remained so to date, and although the patient no longer has claudication or rest pain, there is grave danger of a recurrence following either smoking or local trauma to the extremities. We can

state, moreover, which fingers are in the most precarious condition, as follows: in the right hand the third and fourth fingers especially, and in the left hand the second, fourth, and fifth fingers. These conclusions are based on the arteriographic studies which show the most marked deficiency in the arterial circulation to be present in the fingers mentioned. In other patients it has been possible to predict where the next lesions would occur, in the event of smoking or trauma, with a high degree of accuracy.

#### SUMMARY

The case history of a patient suffering from thrombo-angiitis obliterans with acute simultaneous quadrilateral gangrenous lesions is presented. A search of the literature and inquiry among a number of the major vascular clinics in the United States has failed to reveal a record of any preceding example of this disease with quadrilateral simultaneous lesions.

An outline of what we consider to be the most satisfactory form of therapy for thrombo-angiitis obliterans is included. After considerable experience we have not been impressed with the results from new forms of mechanical apparatus, despite the broad claims which have been made for them.

#### REFERENCES

1. Von Winiwarter, Felix: Über eine eigenthümliche Form von Endarteriitis und Endophlebitis mit Gangrän des Fusses, *Arch. f. klin. Chir.* 23: 202, 1879.
2. Allen, E. V.: Thrombo-Angiitis Obliterans: Methods of Diagnosis of Chronic Occlusive Arterial Lesions Distal to the Wrist, With Illustrative Cases, *Am. J. M. Sc.* 178: 237, 1929.
3. a. Gibbon, J. H., Jr., and Landis, E. M.: Vasodilatation in the Lower Extremities in Response to Immersing the Forearm in Warm Water, *J. Clin. Invest.* 11: 1019, 1932.  
b. Landis, E. M., and Gibbon, J. H., Jr.: A Simple Method of Producing Vasodilatation in the Lower Extremities, *Arch. Int. Med.* 52: 785, 1933.
4. Buerger, Leo: The Circulatory Disturbances of the Extremities, Philadelphia, 1924, W. B. Saunders Company, Chapter LIX.
5. Ito, H., and Asami, G.: Lumbosacral Sympathetic Ganglionectomy: Its Value as a Therapeutic Measure for Thrombo-Angiitis Obliterans, *Am. J. Surg.* 15: 26, 1932.
6. Starr, Isaac: Carbinoylcholine-(Doryl or Lentin). Its Action on Normal Persons, in Peripheral Vascular Disease, and in Certain Other Clinical Conditions, *Am. J. M. Sc.* 193: 393, 1937.
7. a. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco Demonstrated by Skin Temperature Changes, *Proc. Soc. Exper. Biol. & Med.* 29: 487, 1932.  
b. Barker, N. W.: Vasoconstrictor Effects of Tobacco Smoking, *Proc. Staff Meet. Mayo Clin.* 8: 234, 1933.  
c. Maddock, W. G., and Coller, F. A.: Peripheral Vasoconstriction by Tobacco and Its Relation to Thrombo-Angiitis Obliterans, *Ann. Surg.* 98: 70, 1933.  
d. Wright, I. S., and Moffat, Dean: The Effects of Tobacco on the Peripheral Vascular System, *J. A. M. A.* 103: 318, 1934.  
e. Silbert, Samuel: Thrombo-Angiitis Obliterans (Buerger). IX. Surgery, Gynecology, and Obstetrics 61: 214, 1935.  
f. Lampson, R. S.: A Quantitative Study of the Vasoconstriction Induced by Smoking, *J. A. M. A.* 104: 1963, 1935.
8. a. Starr, Isaac, Jr.: A Thermoregulated Foot Cradle for the Treatment of Peripheral Vascular Disease, *Proc. Soc. Exper. Biol. & Med.* 29: 166, 1931.  
b. Starr, Isaac, Jr.: On the Conservative Treatment of Gangrene of the Feet by a Selected Temperature, Oxygen and Dessication, *Tr. A. Am. Physicians* 47: 339, 1932.

## Society Transactions

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### AMERICAN HEART ASSOCIATION, 1937

The thirteenth annual scientific session of the American Heart Association was held on June 7 and 8, 1937, at Hotel Haddon Hall, Atlantic City, N. J.

Dr. E. M. Landis, of Philadelphia, presided at the meeting of the Section for the Study of the Peripheral Circulation on Monday, June 7. The following program was presented.

#### PROGRAM OF THE SECTION FOR THE STUDY OF THE CIRCULATION

**Observations on Phlebitis.** Edward A. Edwards, M.D., Boston, Mass. See page 428.

**The Treatment of Scleroderma by Means of Acetyl Beta Methyl Choline Chloride (Mechoyl) Iontophoresis.** A. Wilbur Duryee, M.D., and Irving S. Wright, M.D., New York, N. Y. To be published.

**The Pathological Basis for Intermittent Claudication in Arteriosclerosis.** J. Ross Veal, M.D., New Orleans, La. See page 442.

**Studies in the Pathology of Vascular Disease.** Milton C. Winternitz, M.D., R. M. Thomas, M.D., and P. M. Le Compte, M.D., New Haven, Conn. See page 399.

**Experiences With the Conservative Management of Sudden Occlusion of Arteries of the Extremities.** Louis G. Herrmann, M.D., Cincinnati, Ohio.

#### ABSTRACT

The important factors in the symptomatology and diagnosis of acute arterial occlusion are emphasized and the mechanism of production of the acute arterial insufficiency after embolism, thrombosis and ligation is discussed. Special emphasis is placed upon vasoconstriction and segmental arterial spasm which is usually present. Vasodilatation must be brought about early to prevent disintegration of tissue while an adequate collateral arterial circulation is being established. The mechanism of the establishment of collateral arterial circulation and the ways of aiding its establishment by drug therapy, controlled environmental temperature, light superficial massage, optimum level of resting extremity, and passive vascular exercises are discussed. The physiological basis for the use of passive vascular exercises is presented with emphasis upon the type of alteration of the environmental pressures most suited to do this work. The danger of excessive heat, elevation, or persistent venous congestion is emphasized, and the four main courses which any acute arterial occlusion may take are shown.

Our experience with twenty-one instances of acute major arterial embolism, twenty-five instances of acute major arterial thrombosis, and nine instances of acute arterial occlusion due to trauma or ligation is presented. In summarizing the results of conservative therapy, only six major amputations were performed in fifty-

three cases. At the end of three months, forty-one patients were living and well. On the basis of our experiences during the past five years, we believe the conservative measures are indicated in most cases of acute arterial occlusion.

**Factors Affecting Vascular Tone** (George Brown Memorial Lecture). Walter B. Cannon, M.D., Boston, Mass. See page 383.

**Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs.** Norman E. Freeman, M.D., Philadelphia, Pa., and Irvine H. Page, M.D., New York, N. Y. See page 405.

**Interpretation of Arterial Elasticity From Measurements of Pulse Wave Velocities.** J. Murray Steele, M.D., New York, N. Y. See page 452.

**The Physiological Effects of Extensive Sympathectomy for Essential Hypertension.** Edgar V. Allen, M.D., and A. W. Adson, M.D., Rochester, Minn. See page 415.

#### DISCUSSION

Discussion of the paper, "Observations on Phlebitis," by Dr. Edwards.

*Dr. Alton Ochsner, New Orleans, La.*—As probably many of you know, Bancroft and his associates for a number of years have attempted, in postoperative cases, to differentiate the potential clotters from potential bleeders; and in a recent communication before the American Surgical Association last week they reported a relatively large series of cases and found that in the cases examined postoperatively approximately 12 per cent were potential clotters. It was in this group of individuals that they believed they could accomplish a great deal prophylactically by giving the patients sodium thiosulphate and also by putting them on a low protein and high carbohydrate diet.

As regards the therapeusis of thrombophlebitis, for approximately five years we have been using leeches. We have revived probably one of the oldest therapies in medicine, and the results have been gratifying. We have had a few more than fifty cases, and it is quite remarkable what can be accomplished if, as soon as the phlebitis occurs—and the sooner the therapy is instituted the better the results—one will apply leeches along the course of the vein. If from four to eight leeches are applied, the number depending upon the severity of the case, usually within five to six hours the pain is completely relieved; within twenty-four hours the temperature has begun to fall, and the convalescence is shortened by weeks.

At the time we made our report three years ago, the suggestion was made that leeches might be used in the treatment of thrombosis of the coronaries. Dr. Lilienthal, of New York, tells me that he has observed two such cases in which leeches were used. Hirudin, which is an active principle of the leech's head, will cause a softening and will dissolve a clot in vitro, which can be demonstrated very readily. The systemic effect of the hirudin is marked as well as the local effect.

Relatively recently in Toronto heparin has been used postoperatively. Dr. Galli informs me that he and his associates, in approximately 300 cases, have used intravenous infusions of heparin postoperatively and have eliminated the incidence of postoperative thrombosis and embolism.

The advantage of Bancroft's work is that one is able to detect these potential clotters. Dr. Lilienthal is so convinced of the efficacy of leeches that he now uses four leeches in every laparotomy. He applies the leeches on the fifth day, and, although his experience has not been large since the institution of this therapy, he believes that he can eliminate thrombosis and embolism.

*Dr. N. W. Barker, Rochester, Minn.*—I was very much interested in Dr. Edwards' excellent paper. He has brought out several points which stimulate further investigation of the somewhat neglected problem of thrombophlebitis.

It is a rather unfortunate commentary on our medical progress that we have discovered very little concerning the etiology of thrombosis and thrombophlebitis since Welch wrote his classical article on the subject in 1898. Welch stated that there were probably three factors concerned in the production of intravascular thrombosis: a local lesion of the vessel which might be degenerative, infectious, or toxic in origin; a disturbance of the clotting mechanism of the blood; and stasis of the blood stream.

Experimental evidence is still conflicting regarding the rôle of direct bacterial injury to the intima of the vein as the starting point for the thrombophlebitis which follows operation, childbirth and severe infectious disease, for it is usually impossible to recover the organisms from the lesion in the vein itself. However, we almost always consider that the lesion of the intima may be caused by a toxin elaborated from bacteria in some distant part of the body.

I would like to ask Dr. Edwards if the evidence of sympathetic stimulation and irritation in femoral and iliac thrombophlebitis has been observed consistently or is an exceptional occurrence.

I disagree with him regarding the harmlessness of the injection of varicose veins in which spontaneous acute or subacute thrombophlebitis exists. I have seen one such case in which a marked extension of the thrombosis into the femoral and iliac veins followed injection of a varix in which there was localized subacute spontaneous thrombophlebitis. Also, I have seen a similar case in which injection was followed by extensive cellulitis of the leg and septicemia.

When one is confronted with a case of thrombophlebitis, particularly if it occur following an operation, one always considers the possibility of a pulmonary embolism. However, the evidence is accumulating that once the clinical signs of thrombophlebitis of the large veins of the leg are definitely manifest, the danger of the thrombus becoming an embolus is very small, approximately 2 per cent in a series which I have recently studied. Conversely, in a fairly large number of cases of fatal pulmonary embolism, in only 4 per cent had there been previously recognizable femoral or iliac thrombophlebitis. When one makes a histological examination of the actual embolus which produces death in these cases, organization at the margins of the embolus is absent. We know that organization of a thrombus in a vein takes place rapidly. Therefore, it would seem that these emboli are detached portions of a relatively fresh thrombus which may have been present only for a matter of minutes or hours. Once the signs and symptoms of clinical thrombophlebitis are present, it is probable that the patient is pretty well protected against the loosening of that particular clot. I have seen only five cases in which fatal pulmonary embolism followed a femoral or iliac thrombophlebitis. In each instance necropsy proved that the embolism did not come from the limb where the phlebitis was recognized clinically but from the opposite limb which previously had not exhibited signs of thrombophlebitis. Therefore, the danger of pulmonary embolism in cases of clinically recognizable thrombophlebitis of the femoral and iliac veins lies in the possibility of the development of an entirely fresh thrombus in a different vein due to the persistence of the same factors which were responsible for the original thrombophlebitis. I believe that this is an important point to be considered in the treatment of these cases.

*Dr. Edwards.*—Dr. Barker has raised the question of the frequency of the phenomena due to sympathetic irritation. Some of the less startling reactions, such as the sweating, are fairly common. Minor degrees of arteriolar constriction giving

coldness are also common. Constriction of the larger arteries as evidenced by coldness and diminution in the arterial pulse is less frequently seen but is not rare. Finally, complete spasm of a major artery, such as a femoral, is rare.

In the treatment of varicose phlebitis, I believe the ligation to be most important. The injections are less important and can sometimes be omitted. I quite agree that using large doses of sclerosing fluid may temporarily increase the *inflammation*, but I have never seen bacteriological evidence of *infection* result. The fluid should be injected in small amounts, and in only one or two areas at one sitting.

Discussion of the paper, "The Treatment of Scleroderma by Means of Acetyl Beta Methyl Choline Chloride (Mecholyl) Iontophoresis," by Dr. Duryee and Dr. Wright.

Dr. Edgar F. Allen, Rochester, Minn.—I wish to compliment Dr. Duryee and Dr. Wright on this contribution. While I have had no actual experience with this method of treatment, I have observed some of the cases treated by Dr. Duryee and Dr. Wright, and it did seem that these patients were improved.

It is to be hoped that the essayists will use some objective method of measuring improvement, but the fact that they have not done so does not discount in any way the results which they have reported.

It has been said that the diminution in circulation in scleroderma is a direct result of the tightening of the skin which interferes with the flow of the blood through the arteries and arterioles. However, arteriography offers evidence that this is not true, for the arteriograms in scleroderma have much the same appearance as do those in uncomplicated Raynaud's disease in which there is no tightening of the skin to interfere with the circulation. Two common findings in both acrosclerosis and uncomplicated Raynaud's disease are absence of the filling of the distal portions of the digital arteries and diminished caliber of these arteries. It appears, therefore, the mechanism of the diminution of the peripheral circulation is the same in Raynaud's disease and acrosclerosis. There is also clinical evidence for this, as many patients with acrosclerosis have vasomotor symptoms indistinguishable from Raynaud's disease, and many patients with uncomplicated Raynaud's disease may develop scleroderma subsequently as a complication of that condition.

At the Mayo Clinic we have had considerable experience with ganglionectomy in the treatment of scleroderma. The results are from good to indifferent, and so many of them are indifferent or poor that one welcomes an additional method of treatment of this very disturbing condition.

I was particularly impressed by the observation pointed out by the essayists that scleroderma improves not only in the areas to which iontophoresis is applied but in other areas as well. This would imply that the improvement is not due to local action but to some general effect.

I should like to ask Dr. Duryee and Dr. Wright if they have tried application of mecholyl by inunction. I should like to ask also if Dr. Duryee and Dr. Wright consider the possibility of the development of sclerosis of the coronary arteries in their patients. It has been shown that repeated infusion of mecholyl into dogs leads to a high degree of sclerosis of the coronary arteries.

Finally, I should like to say that this is a very excellent contribution, and it has been extremely pleasant to hear the subject presented so conservatively and to hear encouragement about this type of treatment.

Dr. Wright.—I will not attempt to answer Dr. Allen's question because Dr. Duryee can do that quite ably. Since Dr. Duryee left New York several days ago, however, I have seen the first patient who I believe has had a more or less serious

relapse following this therapy, and this serious relapse brings up the question as to the mechanism by which this disease is caused, because this woman has been subjected to a very great nervous shock. As we go over our patients with scleroderma, I think we are all impressed with the fact that a considerable percentage of these individuals have been subjected to some rather serious nervous strain preceding the onset of the illness, but even more often, it happens that in the course of the disease they are made suddenly much worse by nervous shocks. This woman had a daughter in a very severe automobile accident, and being assured that plastic surgery would produce a good result as far as the facial deformity went, submitted her to an operation. Instead of success, she discovered within the last few weeks that it is doomed to failure because of infection, and the girl will have many more scars on her face than she had to begin with. This girl being in her early twenties, the mother has taken it very seriously, and the results have been, as I say, the first really serious relapse we have seen during this form of therapy.

From an etiological angle, I think we must conclude, on the basis of this and our other experiences, that central nervous mechanisms, or sympathetic nervous mechanisms, probably play a greater part in the production of this type of phenomenon than local change in the subcutaneous or cutaneous tissues.

*Dr. Geza de Takats, Chicago, Ill.*—We have struggled with the problem of scleroderma, and welcome the suggestion of Dr. Duryee and Dr. Wright that we treat these patients with iontophoresis.

I have tried ganglionectomies with no avail. I have done one parathyroidectomy with negligible results. Our observations on iontophoresis are limited to two cases, but I want to bring out one point as objective evidence of improvement, and that is the measurement of the resistance of the skin to the galvanic current, which can be expressed in ohms and for which measurement some of the more recent instruments are equipped. The last case, which showed a very marked improvement, showed that the galvanic skin resistance dropped from 40,000 ohms to 4,000, which I believe is very definite evidence that there is less thickening of the skin.

The skin contains much more calcium in the affected than in the control regions, but nevertheless we have never regarded these sclerodermic areas as caused primarily by a disturbance of calcium metabolism. I feel that the process is of a chronic inflammatory nature, that calcium is simply deposited there, and it is possible that changes in the parathyroids are just a secondary reaction to the local deposits of calcium.

*Dr. William A. Sodeman, New Orleans, La.*—I think it of interest to report on a patient of Dr. Ochsner's on whom Dr. Burch and I measured the tissue pressure by a direct objective method for determining the pressure in skin and subcutaneous tissues. This patient had had a right cervical sympathectomy and a parathyroidectomy so that we had control on one side of the effect of the parathyroidectomy alone. The tissue tension in this patient was the highest we have ever taken, 338 mm. of water. Two weeks following the operation the patient had marked subjective improvement and objective improvement as well, as far as movement of the extremities and so on is concerned, and the tissue pressure had dropped about 125 mm. of water. The tissue pressure was the same on both sides, indicating that the result was due to the parathyroidectomy and not to the sympathectomy.

*Dr. Duryee.*—In answering Dr. Allen's question as to the use of mecholyl by innunction, I should like to state that we have used it in this manner but not with this group of patients. We have been trying for the last three or four years to develop a simpler slow method of absorption from the skin, but so far our results

have been discouraging. In the future we should control some of these patients by treating them with mecholyl over the unaffected areas to see if we get the same improvement.

The question of coronary sclerosis is important in view of the fact that we have had three deaths in this series. However, in none of the three cases was there any definite evidence that the death was due to coronary disease. One patient died of bronchopneumonia. The other two had electrocardiograms during their time in the hospital, and these electrocardiograms were normal; unfortunately in neither case was there an autopsy.

I am much interested in the work of measuring tissue tension. Dr. de Takats' suggestion of measuring skin resistance adds another objective test for improvement. There is a lot more work to be done in this field before we can really evaluate this form of treatment.

I wish to thank the discussers for their opinions and for their added discussions.

**Discussion of the paper, "The Pathological Basis for Intermittent Claudication in Arteriosclerosis," by Dr. J. Ross Veal, New Orleans, La.**

*Dr. Benjamin Jablons, New York, N. Y.*—We have studied this problem from a different angle, and our results go far to confirm the results which Dr. Veal has presented this morning.

By means of a method which we have termed electromyography, we have applied the principles underlying electrocardiography to a study of muscle function in normal and in diseased individuals, and we have found that normally we get a type of muscle curve which is associated with apparently normal circulation in the muscle.

However, when this circulation is interfered with either artificially or as a result of disease processes, a change in this type of curve occurs, and we have found that by compression, even to a degree where complete obliteration or complete obstruction of the vessel does not occur, a change in the muscle curve is produced; instead of having the normal, monophasic curve, we get a diphasic curve which is always present, even when the compression has not gone to the point of completely obliterating the circulation through the major trunks.

We have found this method of great value in making a diagnosis in early cases of peripheral vascular disease in which there is no obliteration of pulse, in which the oscillometer fails to give you sufficient information to suggest that there is vascular disease, but in which symptoms are present of the nature of intermittent claudication.

*Dr. A. W. Oughterson, New Haven, Conn.*—I am sure we have all been interested in the observations which Dr. Veal has made of the occasional failure of correlation between the degree of obstruction and the presence of claudication, and I would like briefly to call attention to one method of producing claudication, which we perhaps all recognize, namely, the vasomotor spasm.

It is now well recognized that many diseases with vasomotor spasm may result in claudication, but I doubt if it is very widely recognized that in arteriosclerosis also, at least in the early stages, vasomotor spasm may play an important rôle. The incident which first called this to my attention was the temperature studies in an individual with an obstructive, vascular lesion, in which the temperature of the involved limb at rest was higher than that of the normal limb at a room temperature of 68 degrees. However, following exercise the temperatures of the limbs were reversed, the normal limb showed a vasodilatation and the involved limb a vasoconstriction. This would seem to indicate that in the early phases of obstruction, and obstruction which may be due to arteriosclerosis, the vasomotor spasm may explain some of these cases of intermittent claudication, which it is difficult to



explain otherwise. This vasospasm may be manifest only during exercise, and studies carried out on the limb at rest may actually show an increased blood flow in the limb with an obstructive lesion.

*Dr. Feal.*—I would like to thank these gentlemen for their discussion of my paper. There is one point I would add that we have not included in this paper. We have made a series of oxygen saturation studies on these patients and compared these oxygen changes with those found in the normal patient before and after exercise. The oxygen saturation changes are similar in both groups of patients. There was no greater decrease in the oxygen saturation of the venous blood of the claudication cases during their exercise pain than in the normal patients under a similar amount of exercise.

Discussion of the paper, "Studies in the Pathology of Vascular Diseases," by Dr. Winternitz, Dr. Thomas and Dr. LeCompte.

*Dr. Emanuel Libman, New York, N. Y.*—I do not think that it would be proper to let this paper go without discussion. It seems evident that Dr. Winternitz and his associates have opened up an entirely new chapter in the whole subject of the pathology of the blood vessels.

Incidentally, this work makes clearer our conception of the way of development of mycotic embolic aneurysms. It shows that they may originate in infection by way of the lumen as well as by the proved pathway of embolic infection of vasa vasorum.

In the course of the presentation, Dr. Winternitz made very clear the essential differences between the pathology of Buerger's disease and arteriosclerosis. I emphasize this point because papers have appeared in which the lesions of Buerger's disease are classed as arteriosclerosis.

This work may well prove important in also throwing light on the changes in the vessels in cases of acute arteritis. I have no doubt that Dr. Winternitz has thought about that and has ideas on the subject.

*Dr. Winternitz.*—I have nothing to add except to thank Dr. Libman, of course, and to say that I think all aneurysms should be considered anew in the light of the function of the different coats of the blood vessel.

For instance, there can be no doubt that the dissecting aneurysm arises from hemorrhage within the vessel wall; it does not have its origin from a tear of the innermost surface. Mycotic aneurysms may result from embolic processes in the vasa of the vessel wall. One sees evidences of this possibility in the extension of the inflammatory processes to the artery wall from the surrounding tissue. The rate of progression of the process in the surrounding tissue results in many different vascular changes, many of which are exemplified in the tuberculous lung. The rapid occlusions are thrombotic in character; otherwise the vessel would not be obliterated and extensive hemorrhage would be more frequent.

It may be permissible to make one other point. Vessels arising from the intima and dividing into capillaries in the vessel wall, i.e., the intima, have their analogy in the heart valves. Such vasa of the vessel wall may be the portals for mycotic infection leading to aneurysm, and it is conceivable that the vessel arising from the surface of the heart valves may play a similar part in endocarditis.

Discussion of the paper, "Experiences With the Conservative Management of Acute Arterial Occlusion," by Dr. Herrmann.

*Dr. Geza de Takats, Chicago, Ill.*—In analyzing Dr. Herrmann's results, one is impressed by the high percentage of recovery of both limb and life. In fact, in looking over the available literature, the most important of which is the collective

review of the Scandinavian surgeons as shown by Nystrom, it is perfectly obvious that Dr. Herrmann's results are far superior to any results published in the world literature.

You may remember that in the Scandinavian statistics, 60 per cent of a total 382 patients died; 20 per cent required amputation; and only 20 per cent left the hospital with a restored circulation; one-half of these patients were dead in three years.

Now, obviously, the factors that determine the ultimate outcome of a limb affected by a vascular occlusion can be readily grouped into those which are out of our control and those which we can control. We cannot control the condition of the heart, although I will come back to that point in a minute. We cannot control the condition of the vessel wall at which site the thrombosis occurs. We may control the time element, and we can control, as Dr. Herrmann has emphasized, the state of the collateral vascular bed.

In regard to the condition of the heart, under the influence of Dr. Gilbert and Dr. Fenn, who are particularly interested in coronary circulation, I have been impressed with the damage done by digitalization of these patients. Such patients, when an acute embolus occurs, are in a state of shock. It is the consensus of opinion of the medical men working with us in Chicago that a great number of emboli occur because of a sudden overdigitalization of these patients, particularly if the emboli are secondary to coronary occlusion.

I have no opinion to offer on the subject, but just bring this to your attention, because in the last five cases of embolism that I have seen, all of which were multiple, by the time we got to see the patient, the patient had already received massive doses of digitalis although there was no obvious cardiac decompensation.

With regard to the time element, I believe that papers like Dr. Herrmann's, and his teachings, writings, and his active work all around the country will finally give us the opportunity to see these patients earlier. We are not as fortunate in Chicago. I notice that half of his patients had arrived at the hospital (or perhaps they may have been at the hospital) before twelve hours had elapsed. In our material, most of the patients arrive so late that all we can do is to amputate, and I believe that the emphasis on the utmost urgency of seeing these patients early and instituting adequate, conservative treatment will save many lives and many limbs.

The peripheral vasodilatation, as Dr. Herrmann has said, can be accomplished by a moderate amount of heat, by drug therapy, by vascular exercise, and by observing the optimum level of circulatory efficiency. Recently, we have used small doses of sodium nitrite because it acts faster than papaverine and because later on it can be followed by injections of papaverine.

It should be remembered that no drug should be used that will lower general blood pressure to any extent because if it does, it will increase peripheral stagnation in the venocapillary bed.

From all this it would seem, then, that embolectomy is an obsolete procedure. Dr. Herrmann has avoided mentioning under what conditions he would now perform embolectomy, and I feel very strongly, and agree with him, that embolectomy is not indicated, first of all in thromboses; second, it is not indicated if conservative measures succeed, such as he has described, and finally it is not indicated after ten to twelve hours, although there are a number of patients reported, particularly by Dr. Pearse, who have had their circulation restored after twelve hours.

Now the question comes up, should embolectomy be done at all? In my own material, which now comprises fifteen cases of embolism and thirty-five cases of thrombosis, there are only three patients in whom I felt embolectomy should be

done. These were the patients who were seen within ten or twelve hours, and who had shown no definite improvement after conservative measures. I feel that in such cases, with a small exposure under local anesthesia, with adequate equipment, and with adequate, trained assistants, we can do no harm and we may restore circulation.

The only reason I believe embolectomy should not be discarded entirely is that the limb from which an embolus has been removed shows a far better circulation than the limb which has been saved by conservative measures. Dr. Herrmann has dwelt on this in detail. He has said that very often these patients have an ischemic neuritis, muscle atrophy, bone atrophy. These limbs are sometimes so painful and so useless that they have to be amputated, and, when there is a chance of restoring the circulation so the pulse actually becomes palpable and the major arterial pathways are restored, this benefit should be given to the patient.

But I thoroughly agree with him that embolectomy is a complicated, delicate procedure, and in the hands of the casual surgeon can do more harm than good.

In regard to amputations, I feel that, when the patient has been seen twelve, twenty-four or forty-eight hours after the attack, amputations should be urged, because I have in my material some patients who have survived multiple emboli, even though one or two of these emboli have occurred in the brain, and who are now fairly useful members of their community. The attitude still prevails among the general practitioners, among the internists, and also among the surgeons that once the patient has had an embolus and gangrene is present, it is just as well to let that patient die. That is a very faulty view, particularly when you know of some patients who have not only been relieved from their incessant pain and from the danger of sepsis, but whose lives were saved.

I wish to say that I had the opportunity of reading Dr. Herrmann's paper in full, and I am greatly impressed by the excellent results shown by him. They are partly due to his education of the medical profession around Cincinnati, which enabled him to see these patients in a large percentage of cases within twelve hours.

*Dr. Norman E. Freeman, Philadelphia, Pa.*—I am sure that we are all grateful to Dr. Herrmann for the clear presentation of his experiences in the treatment of acute arterial occlusion.

One additional mechanism may be worth considering, and that is the reflex vasoconstriction which occurs after the development of thrombosis or embolism. Constriction of the collateral vessels may determine whether or not the patient will lose his limb or even his life. We do not know whether the vasoconstriction takes place as a local reflex from local trauma to the vessel at the site of the obstruction or whether it takes place as part of the generalized reflex vasoconstriction which is the body's response to any traumatic stimulus. Recent observations on experimental animals have indicated that reflex constriction does occur in collateral vessels. Pharmacological vasodilatation by the use of drugs has been discussed. I should like to stress the importance of the prevention of physiological vasoconstriction. Since it is recognized that traumatic stimuli such as pain, cold, fear, and reduced blood volume produce contraction of the blood vessels throughout the body, control of these factors is necessary in order to assure adequate blood supply to all the tissues of the body. Only in case the general condition of the patient can be brought to its optimum position can the blood flow throughout the entire body be maintained at an adequate level.

I think that it is particularly significant that such a surgical authority as Dr. Herrmann should tell us not to use surgery.

*Dr. H. Vesell*, New York, N. Y.—I would like to ask Dr. Herrmann whether he has any determinations on the blood pressure after the administration of papaverine.

*Dr. J. A. Oille*, Toronto, Ont.—I would like to congratulate the surgeon on an excellent medical paper. It is quite an extraordinary experience. I would also like to ask Dr. Herrmann when he would do an embolectomy.

*Dr. Herrmann*.—For lack of time I have had to omit the discussion of many important points. The point that Dr. Freeman brought up, the general treatment of the patient, is most important and should have been emphasized. Dr. Landis and Dr. Freeman have shown that reflex vasodilatation is an important factor to be considered in this therapy.

The question of when to do an embolectomy and when not to is one which I cannot answer in so many words. I entirely agree with Dr. de Takats when he says that it should be done in a limited number of patients because, when possible, it is the best way of reestablishing circulation. The thing that I am trying to discourage is embolectomy attempted by those who are not equipped to do the operation. It is a very delicate procedure, and the general surgeon who attempts an embolectomy once a year, or once in five years, will do more harm than good. If you are equipped and can definitely localize an embolism, as Dr. Allen and also Dr. Veal have done with the use of thorium dioxide, and then can get the clot out with a minimal amount of trauma, much good will result. The procedure should not be attempted unless it is absolutely necessary.

I feel very strongly that the reason we get good results is because we have the full cooperation of our cardiologists. We sometimes see patients even before they have the embolic occlusion, so to speak, that is, at the first indication of pain, and treatment is instituted before I ever see the patient. Consequently, the stage is set for any type of treatment. Passive vascular exercise is certainly not a cure-all; it does help in certain cases to overcome the peripheral vasodilatation, but the scene must be set if it is to accomplish the best results. I try to emphasize this because you are the people who see these occlusions.

No one questioned my statement that approximately 50 per cent of all arterial occlusions did not result in gangrene. I think you can all remember cases in your own experience where an artery has been blocked; a foot has been pale and slightly painful for a while, and then the condition has disappeared. These things must occur more often than we recognize, and so we must say that 50 per cent will not develop gangrene, but it is with those who do develop gangrene that we must concern ourselves most. About amputation, I wish to emphasize again what Dr. de Takats has said, that amputation must be insisted upon early. I have many patients who have survived embolic occlusion because they had early amputation.

Our problem is to tide the patients over these very serious episodes and to save as many legs as we possibly can. It has been a pleasure to be here today and I am glad the surgeons can contribute to the conservative therapy of such important conditions.

Discussion of the paper, "Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs," by Dr. Freeman and Dr. Page.

*Dr. Harry Goldblatt*, Cleveland, Ohio.—I feel that Dr. Freeman and Dr. Page have made a very important contribution to the study of the pathogenesis of experimental hypertension produced by constriction of the main renal arteries. This demonstration that even total sympathectomy fails to prevent or reduce the hyperten-

sion is the last piece of evidence that was necessary to show that this type of experimental hypertension is not due to a nervous reflex from the kidney and that the nervous part of the vasomotor mechanism does not play a primary or important rôle in its pathogenesis. This centers the initiation of the hypertension upon the reduced blood supply to the kidneys and makes highly probable the existence of a humoral mechanism of renal origin which affects directly the muscle of the arterioles.

Various surgical procedures have been practiced on the nervous system of human beings with hypertension with the idea of reducing the blood pressure. In a certain percentage of cases, no matter what procedure has been used, there has followed a reduction of the blood pressure of varying degree. I see no inconsistency between these positive results and the negative results obtained by the same procedure on this type of experimental hypertension. The two differ in one definite respect. In the experimental type of hypertension the reduction of blood supply to the kidney is effected by reducing the caliber of the main renal arteries by the application of a clamp. In the case of human hypertension the counterpart of the clamp is spasm or narrowing of the renal arterioles due to organic tissue change. No surgical interference with the nervous system can loosen or remove the clamps and improve the circulation to the kidneys. It is only when the clamps are removed or released that the hypertension can and does return to the original level. In the kidneys which are associated with hypertension in man, the musculature of the constricted arterioles might still have the ability to relax in a certain percentage of the cases if the nervous control is removed. This would result in improvement of the circulation through the kidneys. The fall of blood pressure which has been observed may be due to this rather than to an effect on a large part of the vasomotor apparatus in the abdomen.

The fact that these investigators have been able to show that there is no change in the blood volume in this type of experimental hypertension is to me a very significant contribution because it emphasizes the resemblance between this type of hypertension and that which is associated with diffuse vascular disease in man. This means that the study of the pathogenesis of hypertension due to renal ischemia may be of great value because the results may be directly applicable to the pathogenesis of human hypertension.

*Dr. Isaac Starr, Philadelphia, Pa.*—I would like to say a word about the dangers of using ergotamine tartrate as an agent for discovering physiological facts in survival experiments.

It is well known that ergotamine tartrate in pharmacological experiments will reverse the action of adrenalin. It does not seem to be so well known that the dosages required to produce that effect are generally so large that they do not permit survival of the animal.

In the clinical literature there are numerous reports of attempts to secure sympathetic block by doses of ergotamine tartrate which produced little physiological effect. That such block was actually secured has been assumed too easily. There is an easy control of the situation. Workers using this drug must prove that the action of injected adrenalin is blocked. I have repeated some of the clinical experiments in which it was alleged that ergotamine caused physiological effects by means of blocking adrenine, or adrenalin, and after similar dosage, I could detect no blocking of an injected dose of adrenalin. Therefore, it is obvious to me that people using ergotamine in experiments in which the animal survives, must prove that an injection of adrenalin is blocked, before they can draw physiological conclusions.

alone. This allows for confusion in reporting data since only those who are clearly Class I by our criteria have need for any interest in the response of their hearts to pregnancy. The more than ninety-eight per cent of pregnant women who are not Class I never die from causes attributable to the heart.

The results of effort tests vary so greatly under changing conditions—fatigue, anemia, infections, weight changes, fluid intake—that it seems to me that we can hardly expect them to be reliable guides in the prognosis of pregnancy to which so many factors contribute; and that their chief informative value is to show us the importance of these factors in disability and thereby direct our attention to protecting our cardiac patients against such controllable causes of heart failure.

#### Discussion of the paper, "An Injection Study of the Coronary Arteries, Especially in Coronary Occlusion," by Dr. Schlesinger.

*Dr. William J. Kerr, San Francisco, Calif.*—This is one of the most important papers on our program today. Dr. Schlesinger has shown us a very ingenious method of displaying the circulation of the heart. I should like to ask Dr. Schlesinger one question, that is, whether he has had any difficulty in injecting accessory coronary vessels or small ones that come off near the origin of the coronaries.

*Dr. Merritt B. Whitten, Dallas, Texas.*—Dr. Schlesinger certainly has made a decided advance in injection of the coronary arteries. He has made a definite improvement of the method of Gross and Spateholz, and when I see his illustrations I recall some by Spateholz, who illustrated the coronary circulation by diagrams somewhat similar to those of Dr. Schlesinger, but apparently did not actually roll out the heart as Dr. Schlesinger has done.

This new method has the advantage over any method which we have yet seen in that with it we can definitely see anastomosis. Everyone has realized that there are anastomoses in the heart. One can inject one coronary artery alone, and in some cases all the other coronary artery entirely, showing that there is anastomosis, but actually to find the vessel has been a difficult problem. I agree with Dr. Schlesinger that the trouble with Gross' method is that the overlapping of the vessels makes it difficult to tell whether two vessels cross each other or actually anastomose. With the corrosion method, most of the anastomoses are destroyed, but with this new method it seems that we can actually see them.

There are two or three technical difficulties we have to consider in any injection method. If there are post-mortem clots remaining in any of the vessels, these may obstruct the flow and prevent complete injection of the arterial tree. Furthermore, with multiple injections it is important that the injection of the two vessels be simultaneous, otherwise, the injection mass may quickly run through from one artery to the other, and it becomes difficult to locate the anastomotic vessels. I think this method is a decided advance in our study of coronary occlusion and should be used much more extensively at post-mortem examinations.

*Dr. Robert L. Levy, New York, N. Y.*—Dr. Schlesinger's specimens are of great interest in that they portray in graphic fashion many episodes which can be translated into clinical phenomena. I shall only touch upon two. One is the variability in clinical symptoms, which can be readily understood on the basis of these beautiful injections. There takes place, for example, occlusion of a vessel or vessels, which is associated with discomfort; this is followed by the establishment of collaterals, with improvement. Later, there may be closure of other branches, with accentuation of anginal pain. Such a sequence has an important bearing on the attempt to appraise the value of any therapeutic measures which are applied to patients with cardiac pain because it explains the tendency to spontaneous variations in the symptomatology.

angles. Dr. Pardee, of New York, some time ago recommended that the functional capacity test, based on the response of cardiac patients to a certain amount of exercise, be used as a guide in the management of these cases. Dr. Hamilton evidently bases his classification, which is entirely different from the classification advised by the New York City Heart Committee, on the physical findings and laboratory tests.

Each of these methods has its advantages and disadvantages. Dr. Pardee's method is very simple and can be carried out easily in practice. It has, however, many subjective or personal elements. In addition, the classification based on functional capacity is often too changeable; many women entering pregnancy as Class I, may in a few months become Class IIa, and finally, at the end of their term or during labor, be reduced to Class IIb, or III. Furthermore, I have seen cases of Class IIa suddenly developing acute left ventricular congestive failure during labor. On this point I must disagree with Dr. Pardee, who believes that "such things do not happen unexpectedly when the functional capacity grouping is used." The picture of a woman in labor, suffering from pulmonary edema, is so distressing that everything must be done to prevent such a grave condition.

Dr. Hamilton's method is probably more accurate, but it requires a great deal of technical work. Dr. Hamilton uses a more strict and dependable regimen, and I believe, in applying it, we might be able to prevent some of the dangerous cardiac complications in pregnant patients. I do not see, however, why both methods cannot be combined, supplementing each other, and furnishing sufficient criteria for the adequate control of the individual cases.

I should like also to say a few words on the value of full digitalization of patients with signs of congestive failure during pregnancy. I feel that in many cases a serious or fatal breakdown of the circulation is due to insufficient digitalization. If we endeavor to obtain better results, the digitalis treatment should not be left to the obstetrician alone, who is often inclined to use too small and ineffective doses of the drug; strict supervision is necessary. I, therefore, believe that special care and cooperation between the obstetrician and cardiologist in the management of these cases will be helpful in reducing the maternal mortality rate in cardiac patients.

*Dr. Hamilton.*—I am glad Dr. Karp brought up the subject of classification and of effort tests and thank him for his discussion.

Our classification is an outcome of examination of recruits in the World War. The first problem then was to decide what physical signs justified the diagnosis of a seriously damaged heart in a young man and made him unfit for full military service. The criteria for our Class I proved sound for soldiers and have proved sound in selecting women for the risk of pregnancy. Recognizable heart failure does not occur in young adults except among the Class I cardiac subjects. The great variety of factors influencing prognosis in pregnancy has kept us from having confidence in any finer subdivisions of Class I except for the subdivision which we happen to call Class Ia. With improving care in the treatment of Class I cardinals, the need for further classification in pregnancy seems to disappear, while the need for stubborn, continuous supervision of the individual cases becomes more evident. There need be no serious conflict between this classification and the New York classification, provided those using the New York classification apply it to young adults who have the criteria (as for our Class I) which determine that they have in fact seriously damaged hearts. The New York classification does not define the young adult who should be considered a cardiac. As it stands, it suggests that young adults can be classified in respect to their hearts by their functional ability

On Oct. 8, 1936, Dr. Edward D. Churchill, of Boston, resected the pericardium, and in the course of a few weeks the author lost all evidence of his congestion. Since then he has been perfectly well. The venous pressure measurement on Feb. 19, 1937, was 10 cm.

**Acute and Chronic Compression of the Heart** (with motion picture demonstration). Claude S. Beck, M.D., Cleveland, Ohio. To be published.

**Fainting Attacks Resulting From Hypersensitive Carotid Sinus Reflexes** (with motion picture demonstration). Harry L. Smith, M.D., Rochester, Minn. To be published.

**The Use of Quinidine Sulphate Intravenously in Ventricular Tachycardia.** John Hepburn, M.D., and Harold E. Rykert, M.D., Toronto, Ont. To be published.

**The Precipitating Causes of Congestive Heart Failure.** William A. Sodeman, M.D., and George E. Burch, Jr., M.D., New Orleans, La. To be published.

**A Clinical Study of a Preparation of Squill (Urgin) in the Treatment of Myocardial Insufficiency.** Francis L. Chamberlain, M.D., and Robert L. Levy, M.D., New York, N. Y. See *AM. HEART J.* 14: 268, 1937.

**A Study of the Renal Arteries in Relation to Age and to Hypertension.** Robert H. Williams, M.D., and Tinsley R. Harrison, M.D., Nashville, Tenn. To be published.

#### DISCUSSION

**Discussion of the paper, "Multiple Etiological Factors in 5,000 Cases of Heart Disease in Chicago,"** by Dr. Mahner and Dr. Plice.

*Dr. Julien D. Benjamin, Cincinnati, Ohio.*—Will Dr. Mahner please state his criteria for the diagnosis of psychoneurotic and neurotic patients?

*Dr. Paul D. White, Boston, Mass.*—May I add a note on this important and interesting subject, with particular reference to the pulmonary factor. We must carefully distinguish the cor pulmonale, true pulmonary heart disease, which so far as we know is rare although it may be more common than we think at present, from pulmonary symptoms due to congestive failure of the left ventricle, from mitral stenosis with pulmonary congestion, and from pulmonary disease itself. These three types of pulmonary disturbance in connection with heart disease are important to study further. Perhaps as important as any other point would be the more careful judgment of the factors of strain on the right ventricle. Until we have adequate measurement of the true size of the right ventricle, especially its weight, we do not know how common the cor pulmonale is.

*Dr. Mahner.*—The Criteria for the Classification and Diagnosis of Heart Disease was used in classifying patients with psychoneuroses. Many of these patients were also examined by a psychiatrist. This group included patients with neuro-circulatory asthenia and cardiac neuroses.

**Discussion of the paper, "Sixteen Years' Experience With Heart Disease in Pregnant Women,"** by Dr. Hamilton.

*Dr. Louis A. Kapp, New York, N. Y.*—Dr. Hamilton's contribution is of great practical importance to the problem of management of cardiac patients in pregnancy. Due to the difficulty in the proper evaluation of some clinical signs and symptoms during pregnancy, attempts have been made to approach this problem from several



## ABSTRACT

Electrocardiographic manifestations of cardiac conduction disturbances have not been adequately controlled by histopathological studies. Even more confusion exists among the few pathologists who have studied this problem than among physiologists. Between 4,000 and 10,000 serial sections are required to study properly the conduction system of a single heart. A report is made of such a study of several hearts of patients who presented electrocardiographic evidence of intraventricular conduction disturbances. In all cases both bundle branches showed lesions, but one branch was always definitely more involved than the other. The findings in general lend support to the new terminology of bundle-branch block.

Familial Cardiovascular Disease. Jennings G. Olson, M.D., Ogden, Utah. To be published.

The Symballophone: A Modified Stethoscope for the Lateratization and Comparison of Sounds. William J. Kerr, M.D., A. M. Bassett, M.D., M. J. Goldman, M.D., and T. L. Althausen, M.D., San Francisco, Calif. To be published.

Respiratory Changes Produced in the Cardiac Patient by Rebreathing Experiments as Compared With Those of the Normal Individual. Harry Landt, M.D., and Julien E. Benjamin, M.D., Cincinnati, Ohio. To be published.

The Electrocardiographic Changes in Acute Pericarditis: A Clinical and Pathological Study. Joseph B. Vander Veer, M.D., and Robert F. Norris, M.D., Philadelphia, Pa. See *AM. HEART J.* 14: 31, 1937.

The Diagnosis and Treatment of Chronic Constrictive Pericarditis. Orrin W. Pineo, introduced by Paul D. White, M.D., Boston, Mass.

## ABSTRACT

The author presents his experiences as a victim of chronic constrictive pericarditis. In May, 1935, he began to have dizzy spells on exertion, slight dyspnea, and epigastric tenderness. In July, 1935, he noticed that his collars were tight and the veins in his neck were swollen. In August swelling of the lower legs appeared, and he noticed that his belt left an imprint on his abdomen. Digitals was prescribed in October, but it was of no benefit.

For this condition the author presented himself to several physicians. The diagnosis of congestive heart failure was made, and treatment for such a condition was begun, but there was little or no gain except temporarily by rest and the vigorous use of diuretics. Finally, in October, 1936, one and one-half years after the onset of symptoms, it became evident that chronic constrictive pericarditis was the cause of the trouble.

Physical examination showed engorgement of the liver with ascites and dependent edema and increased peripheral venous pressure as indicated especially by prominence of the neck veins and a venous pressure of 23 cm. The electrocardiogram showed normal rhythm, rate 80, with low voltage in all leads, including the chest lead, and slightly inverted T-waves in all leads.

Fluoroscopy showed the heart normal in size and shape. The right border was hazy and poorly defined without visible pulsation. The pulsation of the left border was rather feeble. There was a slight amount of fluid at the right lung base.

strated. The electrocardiograms in cases with combined anterior and posterior infarctions proved at autopsy are shown to illustrate their tendency to assume certain characteristics of the more recent infarction.

The electrocardiograms in the group of cases of myocardial infarction due to an acute thrombosis are contrasted with those in the group of cases of myocardial infarction associated with the more slowly occurring sclerotic plaques. In the thrombotic group the electrocardiograms show the more striking classically described changes in the S-T and T segments. In the sclerotic group the changes are usually not so typical.

Two hundred consecutive cases with four-lead electrocardiograms in which the initial or serial curves showed changes definitely diagnostic of myocardial infarction were studied. On the basis of the electrocardiographic findings in our own autopsied cases and upon the published reports of other autopsied cases and the evidence afforded by experimental studies, these two hundred cases were classified into the following groups: (1) recent anterior infarction type, (2) recent posterior infarction type, and (3) combined anterior and posterior infarction type. The final classification was not made upon any one finding, but upon the weight of evidence furnished by all four leads and the changes observed in the serial curves. Charts are presented to show the detailed analysis of the type of changes in all four leads for each of these types. The value of Lead IV as a diagnostic aid is demonstrated in a large group of cases, especially those with recent anterior infarctions.

**Extracardiac Determinants of the Site and Radiation of Pain in Angina Pectoris**  
With Special Reference to Shoulder Pain. Ernst P. Boas, M.D., and Hyman Levy, M.D., New York, N. Y. To be published.

**Syphilitic Aortic Insufficiency: Clinical and Electrocardiographic Studies. I.**  
Minor Blackford, M.D., and Carter Smith, M.D., Atlanta, Ga.

#### ABSTRACT

Syphilitic aortic insufficiency may develop suddenly by rupture of a gummatous cusp, with death in a few weeks; it may exist at least twelve years without cardiac symptoms. The lesion may be prevented by the prolonged administration of neosarsphenamine in the early stages of syphilis, but it may be precipitated by the injudicious use of this drug in the late stages. The lesion develops sooner after the infection in negroes than in whites. More than half of our patients died within a year after the diagnosis. Of those surviving one year, three-fourths received a large amount of bismuth.

Two or more electrocardiograms were obtained on 50 patients, and single tracings on 80 others. The cardiographic changes paralleled the clinical course in more than half, were directly opposite in about one-tenth, and equivocal in the remainder. The signs of gravest prognosis were splitting and slurring of the QRS complex and progressive low voltage. Arched S-T segments, with high or low take-offs simulating coronary occlusion, were common, but not more common in the group with precordial pain. Finally these electrocardiograms are compared with those of 1,179 patients with other types of heart disease.

**Organic and Relative Insufficiency of the Pulmonary Valve.** Johnson McGuire, M.D., and Ronald J. McNamara, M.D., Cincinnati, Ohio. To be published.

**The Histopathologic Basis of Bundle-Branch Block.** Wallace M. Vater, M.D., Washington, D. C.

Further studies have demonstrated that concurrent diseases frequently exist, such as gallstones, duodenal ulcers, anemias, malnutrition, diverticula of the bowel, pelvic disorders in women, and diabetes. The influence of these agents is questionable.

It would appear desirable to present a portion of the data so far obtained to the members of this association for consideration and critical discussion. The suggestion is offered that the material be presented in symposium form as follows:

- I. Summarization of combination of two or more etiologic factors in 5,000 cases.
- II. Coexistence of rheumatic heart disease with (1) thyrotoxicosis and (2) syphilis.
- III. Coexistence of hypertension with (1) other disease entities; (2) thyroid disease; and (3) syphilis.
- IV. Coexistence of heart disease with other diseases (noncardiac).

Sixteen Years' Experience With Heart Disease in Pregnant Women. Burton E. Hamilton, M.D., Boston, Mass. To be published.

Some Problems in the Diagnosis, Prognosis, and Treatment of Acute Arterial Occlusion. Harold E. Rykert, M.D., and Duncan Graham, M.D., Toronto, Ont. To be published.

An Injection Study of the Coronary Arteries, Especially in Coronary Occlusion. Monroe J. Schlesinger, M.D., Boston, Mass.

#### ABSTRACT

The previous development of an anastomotic circulation, coincident with age, has been used to explain the often-noted lack of correlation between fresh or old complete occlusions of the large branches of the coronary arteries and infarcts of the heart. The incidence of coronary anastomoses has been reinvestigated by a new method, yielding an x-ray picture of all the injectible coronary arteries. These vessels can be studied simultaneously, after projection in one plane without overlapping in the possible anastomotic areas. These x-ray pictures demonstrate the complete lack of anastomoses in elderly hearts without occluded coronary branches. Other hearts of similar age or younger, without infarcts, in spite of numerous completely occluded branches of the coronaries, show rich anastomoses, bridging gaps in occluded branches, but none elsewhere. In hearts containing fresh infarcts, definite, but obviously inadequate, anastomotic channels are seen leading to the infarcted area. On the basis of these observations, it is concluded that anastomoses between branches of the coronary arteries do not increase with the age of the patient, unless coincident with such increase in age, there is also slow occlusion of the branches of the coronaries. Under such circumstances functional anastomoses always develop and to a marked and usually adequate degree.

The Four-Lead Electrocardiogram in Myocardial Infarction and Coronary Insufficiency. Anne Bohning, M.D., and Louis N. Katz, M.D., Chicago, Ill.

#### ABSTRACT

The four-lead electrocardiograms in twenty-five cases of recent myocardial infarction confirmed at autopsy are presented. The characteristic electrocardiographic variations associated with anterior and with posterior infarctions are demon-

much in common. In watching these patients clinically, one can hardly avoid the feeling—and I must say it is only a clinical hunch—that the nervous system is able in certain patients to precipitate hypertension.

Most of the good results seen are in patients who have shown considerable vascular flexibility; in other words, most of them are relatively early cases. This does not always follow; we have had three patients out of eight with malignant hypertension who have been operated on in whom the results, I must say, are brilliant. I would like to close with one other matter. It has impressed me, and I think it is quite an interesting scientific point.

You all know that it was a clinical axiom for years that reduction of blood pressure might interfere with the efficiency of renal function. That dates back to Cohnheim and Traube. How much it has influenced physicians in preventing them from attempting to reduce blood pressure, of course, is anybody's guess. However, when the blood pressure is reduced either as the result of these operations, whether it occur spontaneously or whether it be reduced by various medical measures, such as sodium thiocyanate, the renal blood flow, as measured either by urea or creatinine clearance, remains normal. One would have anticipated that, had the hypertension occurred for the purpose of forcing blood through the kidneys, the renal efficiency should suffer if it were reduced. That is not the case. Furthermore, one might have anticipated insufficient tissue oxygenation throughout the body as a result of sharp fall in blood pressure. That is also not seen. These observations dispose of one of the important objections to reduction of blood pressure as a therapeutic measure, and one of the important modes of thought which have dominated the field of hypertension for many years.

And in closing, I think we have to admit that the Mayo Clinic has contributed importantly to the understanding of hypertension.

Dr. William J. Keay, of San Francisco, presided at the meeting on Tuesday, June 8. The following program was presented.

#### GENERAL CARDIAC PROGRAM

Multiple Etiological Factors in 5,000 Cases of Heart Disease in Chicago. Chauncey C. Mahler, M.D., and Samuel C. Plicke, M.D., Chicago, Ill.

#### ABSTRACT

The "Criteria for the Classification and Diagnosis of Heart Disease" has been an invaluable aid in directing the current of thought of students of cardiovascular disease toward an etiological classification. In statistical studies regarding the etiological factors in various geographic areas, it has been noted by some authors that in single patients two or more causative factors are present. Some of these combinations are relatively frequent, others less so, and many of them are of considerable practical importance.

In a study in the Chicago area of 5,000 cases from varied sources we have found that fully 30 per cent of the patients present the problem of multiplicity of etiological factors.

Rheumatic fever has been complicated with congenital, bacterial, thyroid, hypertensive, arteriosclerotic, and syphilitic factors. The combinations of the rheumatic fever with the thyroid and syphilitic factors have been our especial interest. Hypertension is complicated most frequently by arteriosclerosis, also by syphilis in the negro and thyroid disease in the white race. Many others might be mentioned.

*Dr. Freeman.*—We wish to thank Dr. Goldblatt and Dr. Starr very much for their discussion.

In regard to Dr. Goldblatt's comments, we desire again to emphasize the fact that the central nervous system does not appear to play an essential rôle in the development of hypertension from compression of the renal arteries.

Discussion of the paper, "The Physiological Effects of Extensive Sympathectomy for Essential Hypertension," by Dr. Allen and Dr. Adson.

*Dr. Irvine H. Page, New York, N. Y.*—I think one must admit that Dr. Allen has presented a very impressive array of evidence, and it illustrates, to my mind, one really significant advance that has been made in medicine today: that is the close, generous and honest cooperation among three men, Dr. Adson, Dr. Brown, and Dr. Allen. I think that is important in view of the fact that in study of a subject like hypertension, where the natural history of the disease is so variable, and the interpretation of the symptoms and signs also lead one astray so easily, these three types of minds are willing to cooperate in an adventure and try to pull out of it something really objective. I feel that they have done this. The Society is to be congratulated in having such a beautiful presentation of just this sort of cooperative adventure.

I may point out that Dr. Adson, Dr. Brown, and Dr. Allen have been pioneers in this field, and this is now the third type of operation in which they have been interested, the first one being section of splanchnic nerves with resection of the lower thoracic ganglia, the second, the ventral nerve root resection, and the third, the operation just described.

Dr. Heuer and I have been interested in the effects of splanchnic nerve resection and anterior nerve root resections, and I think in many ways the results from the latter operation agree to a rather surprising extent with this third operation. But I feel that the reduction in operative mortality and the fact that this operation is nothing like so serious as the anterior nerve root section is strongly in its favor. Our results with the splanchnic resections have been distinctly disappointing. That is, there certainly is a sharp drop in blood pressure following operation, and in many cases, striking symptomatic improvement. But during the course of the last year or two there has been a definite return not only of the blood pressure back to the pre-operative level, but return of morbid signs and symptoms. Rare patients appear, however, to be benefited by this operation.

Thus we do not feel very optimistic about supradiaphragmatic splanchnic resection. The results of anterior nerve root resection have, on the whole, I think, been about comparable with the results of the operation which Dr. Allen has just discussed. Some results are extraordinary; others, very poor.

The cause of the changes produced in the patient by this operation is obscure. All of us went into it with the definite feeling that the central nervous system was chiefly involved in the genesis of hypertension. I venture to think that we have all learned that the central nervous system is not so important as we had thought in the genesis and maintenance of elevated blood pressure in certain patients.

However, I think that the tendency to discount the importance of the nervous system is distinctly dangerous. We do not know enough about it yet to discard it. Even though Dr. Freeman and I were unable to find any participation of the sympathetic nervous system in Goldblatt's experimental hypertension, this by no means can be transferred to bedside thinking until proof of the identity of experimental and clinical hypertension is forthcoming. I, personally, believe they have

The second point is related to the specimen shown in which there were multiple areas of occlusion without infarction; sudden death occurred, presumably as a result of the rupture of an atheromatous ulcer. This case illustrates the fact that the heart can carry on although the reserve of the coronary circulation is greatly reduced; but if, superimposed upon such vascular impairment, a sudden accident takes place which further diminishes the reserve to only a small fraction of normal, there results what we have termed "acute, fatal coronary insufficiency." But sudden death is not necessarily associated with the formation of a thrombus or an infarct; dysfunction may be induced by any cause which brings about insufficiency of the coronary circulation. The terminal incident is frequently, but not always, ventricular fibrillation.

*Dr. Schlesinger.*—The question was asked as to the injection of the accessory circulation by this method. In several of the hearts with spontaneous pericardial adhesions, there was no injection outward into the adherent pericardium when the mass was injected into the coronary arteries.

The question of post-mortem clots obstructing the circulation of the mass is very easily checked up on each heart. We always make a complete dissection of the coronary arteries in these hearts after they have been injected. This dissection is absolutely necessary to show which color mass has gone into which vessel and where they have mixed. In this dissection we uncover all ante-mortem and post-mortem clots.

The question about the effect of simultaneous injection of both vessels on the flow from one to the other is an important one. We always start the injection of both vessels simultaneously, slowly raising the pressure to 150 millimeters of mercury and keep it there until it stays constant at that point. Then in all these hearts, in order to disclose any anastomosis which may be present, we lower the pressure on one side to zero, or below, maintaining that in the other coronary at 150 millimeters of mercury, and then reverse this process. When there are no anastomoses present between the two sides, even this extremely unphysiological relation between the two vessels will not force the injection mass from one side to the other. In the 22 normal hearts without anastomoses the same process of reversing and unbalancing the two coronaries was carried out without flow from one side to the other. Of course, at the site of vessels where there are anastomoses, this helps drive the mass from one side to the other.

The question of whether the heart does not really carry on because of the newly developed anastomoses and compensatory circulation is of interest not only in the hearts with occluded vessels. Although I did not bring them along to this meeting, we have a few hearts with enlargement from other reasons, such as hypertension, rheumatic fever, etc., in which there also is a certain degree of anastomotic circulation established in the absence of any occluded vessels. Thus anastomosis between the coronary vessels can occur without occlusion if there is a need in some part of the heart for more blood. This sequence is not as constant as that following the presence of an occluded vessel. We have not had a large enough number of this type of case to say exactly in which condition anastomoses occur, but we feel that anastomoses between coronary arteries always indicates a pathological heart.

Discussion of the paper, "The Four-Lead Electrocardiogram in Myocardial Infarction and Coronary Insufficiency," by Dr. Bohning and Dr. Katz.

*Dr. Sidney P. Schwartz*, New York, N. Y.—Dr. Bohning would have us believe that it is possible by means of serial electrocardiograms to differentiate between a patient with myocardial infarction as a result of an acute coronary vessel closure and a patient with fibrotic replacement of the heart as a result of atherosclerotic narrowing of the vessels supplying that particular region.

As a controlled series for a study of this type, it would be essential to obtain serial electrocardiograms over a period of years on patients with hypertension and enlargement of the left ventricle, to follow such patients to the autopsy table, and to note whether underlying pathological lesions can be correlated with the electrocardiograms obtained. I mention patients with hypertension as controls because the electrocardiogram associated with enlargement of the left ventricle in the course of hypertension would appear from the few studies available to date to show changes somewhat similar to those which Dr. Bohning has presented today as characteristic of patients with myocardial fibrosis.

We have obtained serial electrocardiograms over a period of years on twenty-five consecutive patients with hypertension and enlargement of the left ventricle that have come to autopsy. The electrocardiograms obtained by us are almost identical with those which Dr. Bohning has associated with fibrotic replacement of the heart muscle in the presence of atherosclerotic involvement of the coronary vessels. However, in none of our cases was there either fibrotic replacement of the heart muscle or any lesions of the coronary vessels.

Consequently, I do not believe that on the basis of such observations it is possible in the majority of cases to differentiate from the electrocardiogram those patients who have only enlargement of the left ventricle without coronary vessel involvement from similar cases with fibrotic replacement of the muscle. There is no doubt in my mind from correlated studies to date between the clinical investigations, the electrocardiograms, and the underlying pathological lesions that when infarction or fibrotic replacement of the heart muscle takes place, we have in most instances a very definite pattern in the electrocardiogram such as is well known. Dr. Bohning's ideas, however, remain yet to be proved.

*Dr. Arthur M. Master, New York, N. Y.*—Some of the difficulties of correlating the electrocardiographic findings and even the clinical findings with the pathological findings can be brought out by our experiences recently. We have done what Dr. Saphir and his collaborators suggested. We reviewed some 79 hearts that came to autopsy following death from coronary artery occlusion, and at the suggestion of Dr. Paul Klemperer and Dr. Louis Gross we reexamined and rechecked 42 of the hearts. We made very frequent cross-sections of the coronary arteries throughout their entire course, and in these 42 hearts where previously some 80 occlusions had been reported we actually found 105. We found that even when an acute occlusion is present, 40 per cent had not only one but at least two acute occlusions. We found that where previous occlusions were present, in 80 per cent of the hearts there were at least two or three previous occlusions. The multiplicity of occlusions illustrates the difficulties of correlating the electrocardiographic findings with the location of infarcts. On the other hand, in the majority of cases we had the same experience that Dr. Bohning had. There was correlation. We found, as Barnes has and as Whitten has, that the left anterior descending should not be called the artery of occlusion; that the right artery is as frequently involved as the left; that the posterior surface is as frequently affected as the anterior surface.

*Dr. Bohning.*—In answer to the first question, I think a differentiation should be made as to the electrocardiographic changes related to acute or subacute myocardial injury and those due to chronic myocardial involvement. Most authorities agree that the S-T deviation is related definitely to changes involving the myocardium. The changes due to enlargement and the changes due to the placement of the heart in the chest are, I think, more often related to variations in the form of the T-wave and the QRS complex.

We have made studies with multiple chest leads, going entirely around the chest in a number of cases, both with normal and with injured hearts, and these seem to indicate that there is a great deal yet to be said concerning variations in the electrocardiogram due to changes in the size and position of the heart. We can definitely say, however, that the marked S-T deviation seems to be related to an acute or subacute change, particularly when these deviations tend to decrease or to disappear.

We have also seen a number of cases with myocardial infarctions, especially those with multiple infarctions, in which we could not without earlier curves or an autopsy make a definite diagnosis as to the type of infarction. In our series we had 73 cases of posterior infarct type and 119 cases of anterior infarct type, which would seem to indicate a more frequent involvement of the left coronary artery, but in some of our autopsied cases the right coronary artery was also involved although only anterior infarction was present. Experiments have shown that constriction of the left anterior descending coronary artery produces a relatively greater decrease in total coronary outflow than constriction of the right coronary artery. Therefore, it seems probable that the area of myocardium supplied by the right coronary artery has in most individuals a better collateral circulation than that supplied by the left coronary artery.

Discussion of the paper, "Extracardiac Determinants of the Site and Radiation of Pain in Angina Pectoris With Special Reference to Shoulder Pain," by Dr. Boas and Dr. Levy.

*Dr. Emanuel Libman*, New York, N. Y.—There is a great deal that might be said in connection with this careful and scholarly paper of Dr. Boas and Dr. Levy.

In the first place it is very interesting that they have shown statistically that in the cases of shoulder pain complicating cardiac pain due to coronary artery disease, the pain is mostly on the left side. I am glad that Dr. Boas referred to the exceptions.

How are these shoulder pains brought about? My own idea, for a number of years, has been that there is a metabolic disorder underlying coronary artery disease and coronary thrombosis and that the same (or a similar) disorder plays an important rôle in the pathogenesis of many cases of bursitis, spondylitis, gallbladder disease, eczema, etc. Patients who suffer from coronary artery disease, not infrequently have previously suffered from a shoulder disturbance, usually with limitation of motion. A coronary attack may intensify the condition. In other cases, the shoulder disorder exists in a mild or latent form, and then real suffering is brought about by irradiation (or sensitization) as Dr. Boas has pointed out, when the patient develops the cardiac pain. It is of interest, in this connection, to note that the same sequence of events is occasionally encountered in cases of gallbladder disease, the shoulder difficulty then being on the right side.

What I have said sounds strange, but, if one thinks a bit about it, the impression is a different one. If anybody asks you what is the cause of general arteriosclerosis (atherosclerosis) you will say, if you follow the usual teachings, tension and a metabolic disturbance. The same must hold true for the arteries of the heart.

A patient suffering from the shoulder difficulty which Dr. Boas has so fully discussed, may, if he is hyposensitive to pain, suffer from weakness, with or without paresthesias, instead of pain. It is important to know that the therapeutic maneuver which I employ does not act by decreasing the sensitivity of the nerves. This is demonstrated by the experience that when numbness or weakness is the outstanding symptom of the disorder and not pain, and the method is effective, the whole extremity becomes stronger and any numbness diminishes or disappears.



I feel that I ought to say something about the method itself. I believe it to be valuable, and I am grateful for having found it because it so often relieves suffering.

Firm pressure is applied to Erb's point for about one minute. In some cases less than one minute suffices, in occasional cases a somewhat longer duration of pressure is desirable. After the pressure is released, the patient rests for a minute or two to allow for any pain due to the pressure itself to disappear. Then the patient is asked to raise the arm, and very frequently spontaneous pain is no longer present. This relief may last for hours, days, weeks or months, or for good, even though the original condition persists. The maneuver can be applied repeatedly. If both arms are involved, both sides must be treated separately. It is important, as Dr. Boas has also suggested, to learn how useful the method may be in distinguishing pain in shoulder disorders and those due directly to the heart.

I cannot yet state through what mechanism this maneuver gives the results, but I think that we will find that an effect upon the autonomic nerves plays a rôle. The importance of learning the exact mechanism is self-evident.

*Dr. William J. Kerr, San Francisco, Calif.*—I should like to ask Dr. Boas whether he has studied the relative position of the two shoulders in these patients and whether an encroaching thoracic condition, such as increasing pulmonary emphysema, could play any rôle in the production of the pain.

*Dr. Boas.*—I have not paid particular attention to that point, but as I recall the cases I do not believe that such factors as Dr. Kerr mentioned play a rôle in this syndrome.

I have been rather struck by the absence of similar shoulder pain in galbladder disease although I have looked for it. By analogy, as Dr. Libman suggested, one might expect to find it. While these patients often complain of pain in the trapezius muscle, they do not have this pain in the shoulder which prevents them from moving the arm.

#### Discussion of the paper, "Syphilitic Aortic Insufficiency," by Dr. Blackford and Dr. Smith.

*Dr. Paul D. White, Boston, Mass.*—For some of us in the North who have had much less experience than Dr. Blackford in the diagnosis and prognosis of cardiovascular syphilis his figures may seem a little hard to believe, but I have visited his clinic in Atlanta and can vouch for at least some of these cases. Incidentally, for the first time I heard there a considerable number of Austin Flint murmurs in a single day.

*Dr. Harold S. Feil, Cleveland, Ohio.*—Occasionally one finds patients with evidence of syphilitic aortic insufficiency clinically, and the post-mortem examination reveals cystic medial degeneration with dilatation of the aortic ring. This pathological condition was described by Erdheim and by Moritz. Within the past year, two such patients were observed at the Lakeside Hospital—one patient had latent syphilis and the other patient was nonsyphilitic. Both were young individuals. One cannot say that every patient with free aortic insufficiency and a positive Wassermann has syphilitic aortic insufficiency without bearing this interesting pathological condition in mind. The possibility of its presence should be especially stressed in patients without other evidence of syphilis.

*Dr. Blackford.*—These patients all had syphilis and all free regurgitation at the aortic valve. So far as possible, we fluoroscoped them to exclude calcification of this valve. We believe the error of diagnosis is very low.

Personally, we have only made the diagnosis of dissecting aneurysm of the aorta once (an account of the case will appear in the *Journal of the American Medical Association*), but other physicians at the Grady Hospital have done so four or five times. We are sure that, in spite of the to-and-fro murmur which may be heard in such cases, we have not counted any such as syphilitic aortic insufficiency.

Discussion of the paper, "Organic and Relative Insufficiency of the Pulmonary Valve," by Dr. McGuire and Dr. McNamara.

*Dr. William J. Kerr, San Francisco, Calif.*—Dr. McGuire has presented a very interesting subject and has done it very well. I should like to make a brief remark concerning the murmurs and organic pulmonary insufficiency.

In a limited experience with this type of clinical condition, we have observed a diastolic murmur which Dr. McGuire mentions and have found that it passes down along the sternum more definitely than it does toward the left axilla. Often it is heard best at the xiphoid process, or near there. In addition to the rumbling diastolic murmur, there may be a presystolic murmur which is very much like the Austin Flint murmur heard in aortic insufficiency and also in relative pulmonary insufficiency; with the Graham Steele murmur there may be a murmur of very low intensity heard near the lower end of the sternum, which is also presystolic in time and similar to the Austin Flint. I think that we should keep these murmurs in mind and examine patients for them and try to differentiate them from the murmurs of aortic insufficiency.

*Dr. Maude E. Abbott, Montreal, Canada.*—I am afraid I have not a great deal to add to this subject, for the reason that this is a relatively little explored field of congenital heart disease, at least from the statistical standpoint. We are only beginning now to assemble data upon it.

I was very much interested to see last autumn in Dr. Kerr's own service at the University of California Hospital a remarkable case of aneurysmal dilatation of the pulmonary artery with insufficiency and some stenosis of the pulmonary valve. The etiology of the tremendous dilatation of the pulmonary tract was not clear.

I think the general impression about this type of lesion in this situation is that there is usually some localizing factor that leads to the incidence of an infective process on the pulmonary cusps, or to the occurrence of a relative or organic pulmonary insufficiency. I noticed in the picture of the post-mortem appearances of the second case what looked very like four pulmonary cusps, and I wonder if that might be the underlying factor here in the development of the pulmonary regurgitation.

The subject of pulmonary atherosclerosis is one that is becoming more and more interesting from the standpoints of congenital as well as acquired conditions, and there is still much to be learned in this field. The contribution made by Dr. Roessler to its x-ray study is very important. It is interesting that the second case was, I believe, diagnosed radiologically by him.

I think that is all I have to add, Dr. Kerr. It was very kind of you to give me this opportunity of meeting this assembly on a congenital cardiac topic.

*Dr. Emanuel Libman, New York, N. Y.*—This very interesting demonstration has a number of points of importance. In connection with one of the reported cases, I would like to refer to the case described many years ago by Dr. Edward G.

Janeway. It was a case in which he had clinically diagnosed gonococcal infection of the pulmonary valve. The patient recovered from the infection but was left with pulmonary regurgitation. Perry has reported a similar observation (1930-1933).

I would like, for a few minutes, to take up the subjects of rheumatic lesions of the pulmonary valve, and the Graham Steele murmur. Dr. McGuire has mentioned the work of Epstein and Kugel and that of Dr. Louis Gross. They showed that rheumatic involvement of the pulmonary valve was not as uncommon as was generally believed, the lesion being much more marked in the ring than in the valve flaps. The two cases reported by Dr. McGuire are most unusual because there is present a real rheumatic valvular lesion.

One must be very cautious in predicating the presence of a Graham Steele murmur. I can emphasize that by telling you of a case which I once presented to Dr. Osler, and concerning which he said, "This patient has a Graham Steele murmur, and this is the first one I am at all sure of." The post-mortem examination revealed an aortic insufficiency. When one finds this diastolic murmur which is considered to be evidence of relative pulmonary insufficiency, it is important to examine the valve carefully for predisposing conditions such as thickening or a congenital anomaly of the valve cusps.

*Dr. L. Minor Blackford, Atlanta, Ga.*—Some twenty-five years ago, someone announced that dilatation of the pulmonic cone or trunk was a sure sign of a patent ductus. This statement has been copied blindly in many textbooks.

Actually, almost all of the few proved cases of patent ductus with dilatation of the pulmonic artery have had other anomalies to explain the dilatation. In most cases of dilatation of the pulmonic artery, as in the seven Dr. McGuire has just reported, the ductus is normally obliterated.

*Dr. McGuire.*—I should like to thank Dr. Kerr for explaining the pseudo "Austin Flint" murmur we heard in Case 9.

With regard to the question of congenital lesion of the pulmonary valve that Dr. Abbott has spoken of in the second case, it is our belief that the removal of part of a cusp for section produced an artefact which simulates an extra leaflet. There was nothing to suggest congenital malformation in the original specimen.

**Discussion of the paper, "The Histopathological Basis of Bundle-Branch Block,"**

*Dr. Yater.*

*Dr. Louis A. Kapp, New York, N. Y.*—I note that one of the cases presented by Dr. Yater showed transient asystole with Adams-Stokes attacks. I have also observed at the Bronx Hospital several such cases in which no A-V heart block was found.

I wonder whether the mechanism of production of these attacks cannot be explained by the observation made by Dr. Yater that in practically all cases of bundle-branch block both branches show distinct pathological changes, one branch being usually more affected than the other. When, for some reason, in the less affected branch a severe obstruction in the conduction suddenly develops, the block becomes complete, with possible Adams-Stokes syndrome.

I think that this cause of Adams-Stokes disease should always be considered in the absence of auriculoventricular conduction defect.

*Dr. Paul D. White, Boston, Mass.*—I would like to congratulate Dr. Yater on a very important and difficult job. He has made a distinct advance in our knowledge of bundle-branch lesions and bundle-branch block, even though the last word may not yet have been said.

Discussion of the paper, "Familial Cardiovascular Disease," by Dr. Olson.

*Dr. May G. Wilson*, New York, N. Y.—I think perhaps it might be of interest to report that in a recent study of rheumatic families, we found on genetic analysis of the data that the susceptibility to rheumatic fever was transmitted as a single autosomal recessive gene. The very interesting report of Dr. Olson is of extreme importance.

*Dr. Olson*.—One thing that I plan to do is to report on this family at ten-year intervals. It appears from a study of the first four generations, at least, that the age of onset of the angina is decreasing. I do not at the present time have in this family any record of angina occurring in the third decade, that is between twenty and thirty years. I mentioned the situation in the third generation, most of whom are now living and three definitely had onset in the early thirties.

With respect to the occurrence of rheumatic disease in families, I learned with a great deal of surprise that in Chicago there exists the impression that rheumatic fever does not occur in families. I have had in my practice forty-seven instances of rheumatic disease occurring in the families of mothers who had it.

Discussion of the paper, "The Symballophone: A Modified Stethoscope for the Lateralization and Comparison of Sounds," by Dr. Kerr.

*Dr. Howard B. Sprague*, Boston, Mass.—We had the privilege at the Massachusetts General Hospital of having a demonstration of this instrument by Dr. Kerr some weeks ago, and we were very much impressed with its possibilities. There is one detail that Dr. Kerr might like to mention, and that is, if you have any difficulty in being convinced of what the instrument will do, you must first demonstrate that your hearing is equal on the two sides. Many of us do not realize until we attempt to use an instrument of this sort that the auditory acuity is different on the two sides. I made the unhappy discovery that my hearing was not the same on the two sides, and therefore I had a little difficulty at first in discovering the potentialities of the instrument.

*Dr. Julien E. Benjamin*, Cincinnati, Ohio.—I may be a little stupid, Dr. Kerr, but I do not quite understand why one could not simply attach one end of the stethoscope to one ear and the other to the other ear. Will you explain again why both must be attached to each ear?

*Dr. Paul D. White*, Boston, Mass.—I should like to ask Dr. Kerr when this new instrument will be available for our general use.

*Dr. Kerr*.—Dr. Sprague brought up a point which, of course, is important. If one hears with only one ear, then he might just as well have an ordinary, old-style, monaural stethoscope such as Laennec introduced, and under those circumstances the sound which one hears appears to be directly in the ear.

The binaural stethoscope throws the sound out in space some distance in front of us, and one does not have a loud noise directly in the ear. If the ears are unequal, it would probably throw the sound to one side or the other with this type of stethoscope. It would seem to come from one side or the other, but it would not be any more of a handicap than we have with the ordinary stethoscope.

The question was asked about the direct tubes. If one listens to sounds with direct tubes to the two ears, the sound seems to arise directly in the two ears, and ordinarily it is very annoying. If the sound is of any intensity, it is confusing,

and we have found it difficult to determine small differences with it. We are giving demonstrations at the scientific exhibits and will be pleased to demonstrate this and other points to Dr. Benjamin and others who wish to attend.

I should like to pass around two little membranes or disks which we obtained with two different endpieces for stethoscopes. If you are making up one of these instruments, which you may do rather simply, be sure that the vibration rates of these disks are identical or that they are very close to each other. I am going to pass these around and if you listen with the two, the sounds would be dissimilar.

The instrument is not yet being made and will not be made until we are very certain on all the psychological points. We have most of these cleared up now, but we do not want to put anything out until we know it is reliable, and then we will insist that it be put out at a very low cost. It should not be much more expensive than the ordinary binaural stethoscope.

**Discussion of the paper, "The Electrocardiographic Changes in Acute Pericarditis," by Dr. Vander Veer and Dr. Norris.**

*Dr. Charles C. Wolferth, Philadelphia, Pa.*—Dr. Vander Veer's finding of a correlation between his electrocardiographic changes and myocardial injury is very important. That is not the point, however, that I wish to discuss.

There are at least two clinical conditions in which chest leads should be made in the anteroposterior position as well as with one electrode on the apex and the other electrode on the left leg. Acute pericarditis is one of them. The other is infarction that extends around either from the anterior to the posterior surface of the heart, or vice versa.

The reason, I think, the chest lead selected by Dr. Vander Veer and his colleagues for this study failed to be of much value is that in pericarditis, as a rule, both the anterior and posterior surfaces of the heart are involved. In that particular type of lead, under these conditions, the deviations of the RST segment caused by anterior and posterior injury tend to neutralize each other. If, however, an anteroposterior chest lead is made, the summation of RST segment deviations tends to occur so that one obtains deviations which are frequently much greater than those recorded in limb leads.

*Dr. Roy W. Scott, Cleveland, Ohio.*—It is now ten years since Dr. Feil, Dr. Kutz and I first observed that changes in the ventricular complexes similar to those found in myocardial infarction occurred in patients with pericardial effusion. Both clinical and experimental evidence indicated that the hydrostatic pressure in the pericardial sac was an important factor in distorting the curves. While it seems likely that in certain cases of pyopericardium the associated inflammatory changes in the myocardium may affect the electrocardiogram, I do not believe that in the light of past observations one is justified in concluding that pericardial effusion per se may not cause characteristic changes in the ventricular complex of the electrocardiogram.

*Dr. Vander Veer.*—I appreciate Dr. Wolferth's discussion because he is an authority on the chest lead. There is no question but that Lead V gives a summation effect, as does Lead II, which tends to diminish the changes which one may obtain in the chest lead in this type of case. However, from the practical standpoint, one cannot take three or four chest leads, and it may be, as I think Dr. Wolferth does, a better plan to take Lead IV than Lead V as we have done. We have taken Lead V because it is handier. The patient lies in bed and does not have to roll over or move.

Fundamentally, however, we can differentiate these cases from myocardial infarction without the Leads IV, V and VI because they do not have the patterns that one would expect with a large infarction which involves both anterior and posterior surfaces. So, from the clinical standpoint, if one is aware of the typical pattern, one can diagnose it from the electrocardiogram with the other findings.

Dr. Scott has mentioned their findings of many years ago, and it is certain that the subject is not completely settled. However, I believe that a great deal of evidence points to the association of the electrocardiographic changes with myocarditis. One may see a patient with extreme cardiac tamponade from hemo-pericardium. The heart cannot be heard, and there is no pulse, but there is a normal electrocardiogram. Certainly, if a tamponade was going to produce an insufficiency of coronary flow, it would produce it in those cases. The same patient may be operated upon, and the pericarditis pattern may follow in two or three days. While I agree that the subject is not settled, I believe that in most cases the changes in the electrocardiogram are due to myocarditis.

Discussion of the paper, "The Diagnosis and Treatment of Chronic Constrictive Pericarditis—Orrin W. Pineo," by Dr. White.

*Introduction by Dr. P. D. White*

Mr. O. W. Pineo, a physieist, now twenty-nine years old, has been so kind as to come here today to tell you briefly of his personal experience with constrictive pericarditis and its treatment. He is, to be sure, an outstanding example of the curability of the disease, but as such is far more important for you to see than one of our failures. We have been unusually fortunate in having the majority of the cases of our series resemble him in most respects. His own story he will give you. I shall simply read to you, in closing my introduction of Mr. Pineo, the operative notes written by my surgical colleague Dr. E. D. Churchill early last fall.

"A thick calloused pericardium almost completely adherent to the heart was found at operation. A good line of cleavage was established and ventricles and right auricle were decorticated anteriorly with the freeing of the heart from the diaphragm. Fluid was aspirated from both pleurae. The operation lasted two hours and fifty minutes. He left the operating room in good condition.

"Pathological examination of the excised pericardium showed chronic inflammation without evidence of active tuberculosis or rheumatism. There was no calcification."

Discussion of the paper, "Acute and Chronic Compression of the Heart," by Dr. Beck.

*Professor Jacobaeus, Stockholm, Sweden.*—Mr. Chairman, Ladies and Gentlemen, I first bring you my warmest thanks for introducing me to this meeting. I have heard Dr. Beck's paper with the greatest interest. The condition and the operation are of great interest to us in Sweden, and while we have performed this operation, we have not seen so many cases as you have. I shall take home to our surgeons encouragement to continue this work and to continue their interest in internal medicine. Thank you very much.

*Dr. C. Sidney Burwell, Boston, Mass.*—The first of Dr. Beck's observations which I wish to emphasize is that pericardial obstruction is not a particularly rare condition. Moreover, it is a condition which it is of the greatest importance for physicians to recognize, since, as Dr. White and his colleague-patient pointed out, it is in many instances amenable to skillful treatment. The logical process which

Dr. Beck recommends, of recognizing a physiological mechanism and proceeding from that recognition to a consideration of a disease process, is, I should say, one which is utilized by most of the people who have wide experience with this disease.

Now I should like to ask Dr. Beck his opinion about one point which is not always made clear in descriptions of a disease or descriptions of operative treatment. This question is concerned with the place in the circulation at which the obstruction occurs. When the pericardium is filled with fluid, it is obvious that the compression of the heart is exerted generally. It must involve the ventricles, the auricles, and the intrapericardial portions of the vessels. One sometimes gets the impression from reading the older literature that the obstruction from scar often comes about through constriction of one of the vena cavae. If constriction of the venous channels were important, one would expect to find occasionally a difference in the pressure in the inferior vena cava as compared with the superior caval system. In a considerable number of cases in which comparable measurements have been made, we have not seen a case in which such a difference existed except when some obvious local cause for it was present.

If I understand Dr. Beck's description, it implies that he considers the important point of obstruction to be in the pericardial scar involving the ventricles themselves. This agrees with the general concept that the difficulty in constrictive pericarditis is the inability of the ventricle to dilate adequately. If this theoretical concept is true, it should be demonstrable by a simple experiment. If the heart cannot dilate and its output per beat is fixed at a low level, then the only way the cardiac output per minute can increase is by the acceleration of the pulse rate. This being so, if the pulse rate be accelerated, for example, by atropine, one might expect the venous pressure to be reduced. This is in fact the case. When by the use of atropine the heart rate of a patient with constrictive pericarditis was elevated from 80 per minute to 120 per minute, the venous pressure fell to a significant degree. This I think bears out the theoretical concepts which have been so ably presented here.

*Dr. Beck.*—I have nothing further to say. I fully agree with Dr. Barwell's point of view as to the common source of the compression. It usually is over the entire heart, in my experience at least, and I think it is important for the surgeon to determine where the compressing agent is performing most of its compression. It usually is, but it may not always be, generalized over the ventricles. We have produced experiments in which the chief compression was over the right auricle. It is necessary for the surgeon to know exactly where the compression agent is functioning most, because in certain cases the surgical course is to the right of the sternum and not to the left, and, if you go in to the left of the sternum and find the right auricle compressed by a thick scar which has to be taken away to get exposure, you have to use a bilateral approach, including an approach on the right side of the sternum, which adds to the magnitude of the operation. I have done a few operations from the right side because we wanted to have a good exposure of the right auricle and right ventricle.

Discussion of the paper, "Fainting Attacks Resulting From Hypersensitive Carotid Sinus Reflexes," by Dr. Smith.

*Dr. William J. Kerr, San Francisco, Calif.*—We had one of the most striking examples of this sensitive reflex in San Francisco not long ago. Dr. John Musser was giving a dinner lecture on coronary occlusion, and one of our older, more obese

doctors who had not worn his dinner jacket for perhaps two or three years, came to this dinner and his collar was much too tight. He had a most remarkable attack which suggested an Adams-Stokes syndrome.

*Dr. Soma Weiss, Boston, Mass.*—Probably the most important and interesting part of the problem is presented by the group that we have studied in recent years, one that we named the "cerebral type." In this group, one finds syncope and convulsions, in spite of the fact that there is no cardiac slowing and no fall in the blood pressure. This group was described clinically by the English neurologist, Gowers, who considered these problems as being borderline between epilepsy and syncope. In this group, apparently the hyperactive carotid sinus reflex impulses produced inhibitions in certain vegetative centers. At least, that is the only conclusion that we can draw because the systemic blood flow, as well as the blood flow through the brain, remains normal.

To us, in addition to the practical points brought out by Dr. Smith, the most important aspect of the problem was that here is given an opportunity to study unconsciousness under controlled conditions. We have made various assumptions, in the past, as to the cause of unconsciousness and convulsions in human beings; but from the observations that we have made as to the physiology of unconsciousness, we can conclude that in man unconsciousness is caused by a number of different mechanisms, and among these mechanisms cerebral anoxia is only one. Nervous impulses and other factors play an equally important and probably a more important rôle.

*Dr. John P. Anderson, Cleveland, Ohio.*—I have observed unconscious attacks to follow carotid sinus pressure in some patients but in others have noticed no response.

In some instances the attacks followed pressure on the eyeball and in some patients, merely holding their breath would induce an attack. Some of them had their attacks at night when they would empty their bladders.

I should like to ask Dr. Smith if he thinks there is anything specific about the carotid sinus pressure.

*Dr. Harry L. Smith, Rochester, Minn.*—I am unable to answer this question positively, but in my experience there was not a constant correlation between the changes in respiration and heart rate and the syncopal attacks. Quite often, in the induced attacks, we did get rather striking changes in respiration. The most important changes noted were deep and labored respirations. These usually came on early, but in the induced attacks the patient might not lose consciousness, and there might be very few or no changes in the cardiac rate. In other words, there was no constant and definite correlation between the changes in respiration and heart rate and the syncopal attacks.

In answer to the second question—I have not induced attacks by making pressure over the eyeball. I would advise strongly against this practice as I do not think it is wise to make firm or continued pressure over the eyeball to induce attacks. The eye is a very delicate organ, and definite damage to the eyeball might result from the procedure.

Discussion of the paper, "The Use of Quinidine Sulphate Intravenously in Ventricular Tachycardia," by Dr. Hepburn and Dr. Rykert.

*Dr. Paul D. White, Boston, Mass.*—This is a method of treatment that has certainly not been used much. We should all have it in mind when we encounter similar cases, for occasionally it may be life-saving.



Discussion of the paper, "The Precipitating Causes of Congestive Heart Failure,"  
by Dr. Sodeman and Dr. Burch.

*Dr. C. Sidney Burwell, Boston, Mass.*—I should like to draw one more moral from this interesting paper of Dr. Sodeman and Dr. Burch. This moral concerns the relation of the precipitating causes of heart failure to the management of patients with asymptomatic heart disease. The events which have, in the patients described by these authors, precipitated the onset of symptoms of heart disease have been in general events which increased the work of the heart. What is much more important, they have been, on the whole, events which are under a considerable degree of control on the part of the patient and his physician. The object of the treatment of heart disease is the prolongation of effective life. This being so, the adequate understanding and control by the physician of these precipitating causes is one of the most important things that can be carried out in dealing with the great group of people who have heart disease, but who have not yet developed heart failure. In these people, the problem is not that of the treatment of heart failure or cardiac pain, but the postponement of the onset of heart failure. This postponement is influenced more by the control of precipitating causes than by any other single factor except the advance of the underlying causative disease.

*Dr. Louis F. Bishop, Jr., New York, N. Y.*—I should like to ask what type of exercise was noted among the precipitating causes.

*Dr. Sodeman.*—Exercise in these patients varied, of course, and was usually the patient's work or some unusual activity which was carried out by the patient.

I wish to thank Dr. Burwell for his comments.

Discussion of the paper, "A Clinical Study of a Preparation of Squill (Urginin) in the Treatment of Myocardial Insufficiency," Dr. Chamberlain and Dr. Levy.

*Dr. William D. Stroud, Philadelphia, Pa.*—For the past year the concern manufacturing urginin has asked us at the Pennsylvania Hospital to try this drug in the heart clinic, and our reply has always been that since Dr. White and Dr. Marvin studied these other preparations similar to digitalis and had come to the conclusion that there was nothing they could do that digitalis could not do, that was the law and should stand.

But finally, having studied these digitalis preparations for the last six years, we felt we had a series of cases which warranted comparison, so Dr. Vander Veer and Dr. Dominick for the last few months have been transferring a number of these patients who have been taking various digitalis preparations for the last six years to urginin. I hesitate to discuss Dr. Chamberlain's and Dr. Levy's paper, since we have not come to definite conclusions which we can prove statistically, so this discussion must be taken with reservations.

I am just a little fearful that you may all go away from this meeting, after the summary which Dr. Chamberlain read, and shift your patients, now taking digitalis, to urginin. I urge you not to do this too precipitously since our impression is that this drug is not as universally potent in its action on patients with auricular fibrillation, whom we have been following for these past few years while taking various digitalis preparations.

I should like to ask Dr. Chamberlain if he feels there are many patients who cannot maintain their maximum circulatory efficiency on digitalis without developing toxic symptoms. In a group of such patients who cannot maintain circulatory efficiency without giving sufficient digitalis to give toxic symptoms, are there many who, transferred to an equivalent amount of urginin, will not develop

toxic symptoms? In other words, are there many patients with cardiovascular disease and borderline failure, who can take urginin without toxic symptoms, but will develop toxic symptoms when given an equivalent amount of digitalis.

*Dr. James G. Carr, Evanston, Ill.*—We worked with this preparation at the County Hospital and at the Evanston Hospital over a period of some four or five years before we offered anything for publication. Our detailed work is not so good as the work that has been presented here this afternoon, but we were convinced as a result of our work that a certain number of individuals who take digitalis with difficulty can be well controlled with the use of urginin.

Three cases which I followed over a period of some years come to my mind now. All of these patients were unable for one reason or another to take digitalis. Whether it was because they thought they could not take digitalis I am unable to say, but I do know that the cases had been given up by the physicians in charge and we were allowed to try the scillonin, under which name the drug was known at the time. Of these three patients, two are still living after seven and six years, respectively, following the first dose of the urginin preparation. We do not believe that the drug differs in any particular way from digitalis. It is of no greater value to the patient than is digitalis if the patient can take digitalis with comfort.

We found we could give to patients who had not taken any digitalis preparation within the last two weeks, from 8 to 12 mg. within four days without producing intoxication. The daily maintenance dose is 0.5 mg. or less. In one respect our results differed from those reported by Dr. Chamberlain and Dr. Levy. Our experience led us to believe that ectopic beats are usually the first sign of intoxication. We felt after we had worked with the drug for some time that patients who began to complain of nausea should have the drug withdrawn promptly as such patients were likely to develop rather pronounced signs of intoxication if the drug was continued.

On the basis of a considerable experience, 104 courses in 85 patients if I remember correctly, I believe that this drug is of value, not because it is better than digitalis, but because a certain number of people find it difficult to take enough digitalis to restore compensation.

*Dr. Soma Weiss, Boston, Mass.*—I would like to recall that, in spite of the fact that a number of digitalis preparations have been introduced in therapy during the last twenty years, so far it has not been proved that any of these preparations is, from a clinical point of view, superior to digitalis leaf itself.

If we remember that all digitalis bodies are quantitatively synergistic with each other, and if we further remember that the therapeutic effect depends on cardiac toxicity (cat unit), on the one hand, and on the persistence of action (rate of elimination) of these digitalis preparations on the other hand, plus the degree and type of failure of the circulation, then it will become clear that the variation in the clinical response to digitalis preparations depends more on these factors than on the specific pharmacological characteristics of the preparation itself.

In other words, this very interesting and valuable contribution has shown that urginin acts like digitalis. It did not show, and as I understand it is not claimed, that it is a better agent than digitalis. Whether in the few instances where no untoward manifestations occurred this was due to the fact that urginin, in contrast to digitalis, does not cause or induces less nausea or vomiting, or whether as a result of the difference in the persistence of action of the two drugs, relatively smaller doses of urginin were given, in spite of the fact that the doses expressed in cat units were similar, it is difficult to say.

So my conclusion is that as long as it is not definitely established that a preparation is better than digitalis, and as long as we know a great deal about digitalis purpurea, it is wiser to stick to that simple preparation rather than to use a drug which is more expensive and less well understood.

*Dr. Chamberlain.*—It is difficult to compare the action of two drugs in a condition so variable in its course as congestive heart failure. Our observations indicate that urginin shows no superiority over digitalis with respect to its action in cardiac insufficiency. The place to use urginin, at least for the present, is in those patients who, because of idiosyncrasy or prejudice, are unable to take digitalis without discomfort. There were some ten patients in our series who supposedly had an idiosyncrasy to digitalis and by whom urginin was well taken. Later, on administering digitalis, either by injection or in a form which they did not recognize, their idiosyncrasy was found to be imaginary. There were two patients, however, who definitely could not tolerate digitalis and who were able to take urginin without unpleasant effects.

# Department of Reviews and Abstracts

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## Selected Abstracts

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Radnai, P., and Mosoyni, L.: Vasoconstrictor Pulmonary-Coronary Reflex. *Ztschr. f. d. ges. exper. Med.* 98: 651, 1936.

Injection of starch suspensions in the ear veins of the rabbit causes only pulmonary emboli. None appears in the heart. Yet five to six minutes after such injections the electrocardiogram shows evidence of acute coronary closure. This is interpreted as a reflex closure from the lungs. When the vagi are sectioned, these electrocardiographic findings are absent. The vagi are, the authors conclude, the path of the afferent pulmonary fibers and efferent coronary fibers. Both atropine and amyl nitrite prevent this reflex from occurring. The application of these results to the clinical understanding of pulmonary embolism and angina pectoris is emphasized.

L. N. K.

Wahren, H.: O<sub>2</sub> Consumption in Postoperative Shock. *Ztschr. f. Kreislaufforsch.* 29: 149, 1937.

O<sub>2</sub> consumption is decreased in the entire animal (cats) following shock, and O<sub>2</sub> tension in a subcutaneous gas bubble decreases at the same time that CO<sub>2</sub> increases.

L. N. K.

de Carrasco, O., and Zaeper, G.: The O<sub>2</sub> Dissociation Curve of the Blood and Circulation. *Ztschr. f. Kreislaufforsch.* 29: 157, 1937.

The authors correlated O<sub>2</sub> dissociation curve of blood with O<sub>2</sub> utilization. It is pointed out that the normal O<sub>2</sub> dissociation curve is such as to make O<sub>2</sub> exchange inadequate during muscular work and in abnormalities of the circulation. A shift of the curve to the right occurs in these conditions and permits an adequate O<sub>2</sub> exchange with the tissues. This is due to a change in the state of the hemoglobin, presumably the result of CO<sub>2</sub> excess and pH change in the blood.

L. N. K.

Lederer, E.: Capillary Circulation Studies. I. Fundamentals, Methods. *Arch. f. exper. Path. u. Pharmacol.* 182: 363, 1936.

The circulation time in 0.4 limbus capillaries averaged 1.6 to 2.4 seconds in 12 healthy children. Readings repeated at a single sitting varied from 0.2 to 0.8 second which represents the physiological range of changes. The repeated readings over several weeks showed no greater fluctuations than in successive readings at one sitting.

L. N. K.

Ehrström, M. C.: Metabolism of Blood and Urobilinuria in Insufficiency of the Heart. *Acta med. Skandinav.* 88: 517, 1936.

Ten cases of heart failure were studied. A reversible reticulocytosis during failure was found. This is associated with an increased total urobilin production. The urobilinemia is paralleled by a urobilinuria. Hemolysis is the cause of this change in pigment metabolism in heart failure.

L. N. K.

Faleiro, A.: "Exercise Test" in the Electrocardiographic Diagnosis of Angina Pectoris. *Deutsches Arch. f. klin. Med.* 179: 238, 1936.

In this presentation, 60 patients with typical stenocardia and 250 patients with a questionable diagnosis were studied. A test was considered positive when a depression of 1 mm. of S-T in Lead I (and II) occurred, when T became flattened or inverted or when S-T became abnormally elevated following exercise. Thirty-two per cent of the cases with definite angina showed this positive exercise test. None of the cases with a questionable diagnosis gave a positive exercise test.

L. N. K.

Brandt, W., and Reindell, H.: The Electrocardiogram of the Isolated Frog Heart Under Influence of Light and Heavy Water. *Klin. Wehnschr.* 15: 260, 1936.

Studies show that Ringer solution having less than 5 per cent of deuterium oxide has no effect whereas concentration of this substance of 10 to 20 per cent has a measurable effect, and concentrations of 50 per cent have a marked effect on perfused frog hearts. This is manifest in a decreased amplitude, prolonged A-V conduction time, prolonged systole, and a decrease in the rate of beating. Total A-V block may appear. These changes can be reversed by substituting ordinary Ringer solution. Apparently, the deuterium oxide acts to show metabolic processes.

L. N. K.

Kahlstorf, A.: Heart Size in Paroxysmal Tachycardia. *Klin. Wehnschr.* 15: 1028, 1936.

A case of paroxysmal auricular flutter with 1 to 1 conduction and auricular rate of 280 was observed in the roentgenkymograph two hours after the onset of the paroxysm. Enlargement of the heart, decrease in size of the blood vessel shadow, and venous stasis were found. It is interesting that the kymograph gave an idea of the mechanism in this case. The author suggests the use of the roentgenkymograph to determine the origin of paroxysmal pacemakers.

L. N. K.

Rühl, J., and Spiegl, E.: Concerning Interference of Two Excitation Waves in the Ventricle. *Med. Klin.* 32: 841, 1936.

The electrocardiographic appearance of a beat resulting from fusion of the impulse from a late diastolic ventricular extrasystole and impulse transmitted through from the sinus node is described.

L. N. K.

Eckey, P.: Electrocardiographic Changes in So-Called Cor Nervosum. *München. med. Wehnschr.* 83: 1051, 1936.

The author concludes from his studies that the electrocardiogram sometimes may be misleading in differentiating organic heart disease from the so-called functional heart disorders.

L. N. K.

Herzog, E., and Rodriguez, H.: Involvement of the Myocardium in Exanthemata (Myocarditis Exanthematica). *Beitr. z. path. Anat. u. allg. Path.* 96: 431, 1936.

In exanthemata only enlargement of the left ventricle occurs grossly, but microscopically 97 per cent shows disseminated diffuse interstitial myocarditis with perivascular (capillary and precapillary) cellular invasion consisting of fibroblasts, plasma cells, lymphocytes, and polymorphonuclear leucocytes. The capillary walls are swollen and inflamed. Leucocytes occur early in the disease and lymphocytes later. Myocardial degeneration is rare. Involvement of the conduction system was found 3 times in 13 cases examined. This consisted of leucocytic infiltration and fatty degeneration of some fibers of the left bundle. The electrocardiographic changes resemble those seen in diphtheria.

L. N. K.

Oille, John A.: Differential Diagnosis of Pain in the Chest. *Canad. M. A. J.* 37: 209, 1937.

The author discusses the differential diagnosis of pain in the chest as a symptom of cardiac disease. The observations are based on a group of 225 patients selected from a large group of 600 cases seen in practice. There is a full description of the various features of cardiac pain, especially as it relates to a diagnosis of coronary thrombosis. The article is unusually interesting from a clinical standpoint in interpreting this important symptom.

H. McC.

Gouley, Benjamin A., McMillan, Thomas M., and Bellet, Samuel: Idiopathic Myocardial Degeneration Associated With Pregnancy and Especially the Puerperium. *Am. J. M. Sc.* 194: 185, 1937.

A clinical study was made of seven women having cardiac decompensation in the puerperium. Four of these patients died, and at necropsy showed a myocardial degeneration differing from the lesions ordinarily associated with the current classification of heart disease.

The coronary arteries were normal and there was no evidence of coronary occlusion in the living patients.

Death occurred in three cases following embolism, which had its origin on the endocardial surface of degenerated heart muscle. No other proven source of embolism was found.

Pulmonary and cerebral embolism were notable. Slight patency of the foramen ovale, apparently due to recent pressure changes within the right auricle and allowing the passage of a pencil, was present in one instance. No patency was demonstrated in the three remaining cases.

AUTHOR.

Friedman, R.: Effect of Valvular Deformities on the Duration of Life. *Ztschr. f. klin. Med.* 130: 382, 1936.

Statistical analysis is presented of rheumatic hearts in Vienna—a total of 1,164 cases. It was found that 67.5 per cent had the first rheumatic manifestations in the first two decades of life. Mitral valve and combined valve involvement were commonest. A combination of mitral stenosis and insufficiency was the rarest of the mitral defects. Eighty-three and five-tenths per cent of the patients died because of valve defects or their sequelae. The death rate increased until the fifth decade. Heart size plays an important rôle in prognosis. The work is in accord with that in American literature.

L. N. K.

Levine, Harry B., and White, Paul D.: Pulmonary Infarction Complicating Severe Disease of the Mitral Valve. *Arch. Int. Med.* 60: 39, 1937.

We report here 5 cases of severe disease of the mitral valve with congestive failure having as a fatal complication pulmonary infarction without any clinical syndrome of sudden vascular collapse or any similar episode. Autopsy was performed in each case.

Analysis of the incidence of this complication in a series of 52 cases of mitral stenosis noted in 2,500 records of autopsies at the Massachusetts General Hospital showed that pulmonary infarction occurred in 61 per cent of 23 cases in which there was congestive failure and in only 7 per cent of the cases in which congestive failure was not present. In a comparative group of 82 cases of hypertension noted in the records of 1,400 autopsies at the Massachusetts General Hospital, there were 39 cases of congestive failure, in 21 per cent of which there was pulmonary infarction.

Pulmonary infarction complicating severe disease of the mitral valve with congestive failure is not uncommon. This condition is sometimes difficult to diagnose; it makes treatment of the congestion very difficult, and it renders the prognosis grave.

AUTHOR.

Greishaber, H.: Situs Inversus of Abdominal Organs With Congenital Heart and Right Sided Aortic Arch. *Schweiz. med. Wchnschr.* 52: 1307, 1936.

In spite of right-sided aortic arch and situs inversus of the abdominal organs, there was no dextrocardia. The heart had a septal defect. The low position of the left side of the diaphragm in this case despite the left-sided position of the liver indicates that this is caused by the heart. The liver does not, therefore, normally elevate the right diaphragm. The case had a mirror image of normal in Lead I in spite of the absence of dextrocardia.

L. N. K.

Borgard, W.: Congenital Anomalies of the Aorta. *Ztschr. f. Kreislaufforsch.* 29: 216, 1937.

A case report is presented of stenosis of the aortic arch between the origins of the left carotid and the left subclavian arteries, with typical x-ray findings and an abnormal electrocardiogram with left ventricular preponderance. The diagnosis is made on these findings plus the clinical signs of absence of pulsations in the lower extremities of a relatively smaller pulse in the left than the right radial, of the presence of collaterals on the right upper chest posteriorly, of a systolic murmur over the pericardium, and of cardiac enlargement.

L. N. K.

Messeloff, Charles R., and Pomerantz, Anne: A Study of Lead IV in Normal Children and in Ambulatory Children With Cardiac Disease. *Am. J. Dis. Child.* 53: 1485, 1937.

Lead IV in the electrocardiograms of children is characterized by a marked variability in the form and in the direction of its several compounds.

Upright, diphasic, and iso-electric, as well as negative T-waves are normal findings in the tracings of children.

In the present series of tracings for ambulatory children with heart disease Lead IV supplied no information which was not secured from the three standard leads.

This study provides no justification for the routine use of Lead IV for ambulatory children with heart disease.

AUTHOR.

Wilson, Robert, Jr.: Studies in Syphilitic Cardiovascular Disease. Am. J. M. Sc. 194: 178, 1937.

Two hundred and eleven cases of syphilitic aortitis, proven at autopsy, have been analyzed with regard to presenting symptoms. In practically every case in which cardiac or respiratory symptoms were present, they have been shown to be due to some factor other than uncomplicated syphilitic aortitis—either to an extension or complication of the syphilitic process or to some coexisting disease. It is concluded that uncomplicated syphilitic aortitis is an asymptomatic condition, and that no criteria dependent upon symptoms are reliable in making an early diagnosis.

AUTHOR.

Cossio, P., Vivoli, D., and Caul, H.: Syphilis of the Interventricular Septum and Ventricular Tachycardia. Am. J. M. Sc. 194: 369, 1937.

This report deals with a case of ventricular tachycardia caused by a syphilitic lesion of the interventricular septum.

It was a typical attack of ventricular tachycardia due to infarction of the interventricular septum.

The lesion was of the sclerogummatous type with endocoronaritis, and *Treponema pallidum* was found in it.

This observation, as far as we know, is the first of its kind in medical literature, and shows that a syphilitic lesion of the septum is able to produce an attack of ventricular tachycardia. In a case of prolonged attack of ventricular tachycardia, provided that the Wassermann and Kahn tests are positive, we must not only suspect infarction of the septum of the ordinary type, but also one of syphilitic etiology.

AUTHOR.

Potthoff, F.: Tuberculosis and Heart Size. A Study of 600 X-rays of Men With Tuberculosis. Beitr. z. klin. d. Tuberk. 88: 187, 1936.

A large number of tuberculous patients show definitely smaller hearts than normal. Only in severe tuberculosis does brown atrophy occur. The small hearts are therefore hypoplastic and may be associated with the patient's constitutional makeup. In the present series, 88 per cent had hearts smaller than normal (the normal series used being that reported by Hammer).

L. N. K.

Weber, H.: Early Diagnosis of Arteriosclerosis. Med. Welt. 10: 928, 1936.

The most common site of early arteriosclerosis is in the coronary arteries. This may give evidence of heart failure in the form of tachycardia and shortness of breath. It is not easy to demonstrate this arteriosclerosis by roentgenogram. Consequently many years may elapse before the arteriosclerosis is diagnosed clinically.

L. N. K.

Gerstner, H.: Action of Electrical Currents Upon the Blood Pressure. Arch. f. exper. Path. u. Pharmakol. 185: 184, 1937.

Direct current and alternating current of various frequencies and strengths were applied to anesthetized dogs. Arterial blood pressure and pressure within the abdominal cavity, used as an index of general muscular tension, were recorded simultaneously. He was not able to demonstrate narrowing of the peripheral vessels apart from that due to tension of tetanized muscles. Gerstner found that, as



current was increased, first a rise in blood pressure occurred which appeared to be simultaneous with onset of muscular contraction. Then due to marked slowing of the heart, ending in final stoppage in diastole, occasionally to ventricular fibrillation, a sharp fall occurred. When stimulation with the strength of the alternating current constant but with gradually decreasing frequency of oscillation was used, observable effects on blood pressure or striate muscle did not occur until the frequency fell to 2,000 cycles per second. Arterial pressure then rose but not until 50 cycles per second was reached did the heart stop and fall in pressure occur.

J. M. S.

Neuhaus, F.: Relation of Adrenal Adenoma in Hypertension. *Beitr. z. path. Anat. u. z. allg. Path.* 97: 213, 1936.

Seven hundred adrenals were examined. The adenomas were twice as common in hypertensive persons as in those with normal blood pressure. Adenoma of the adrenal is considered a sequel and not a cause of hypertension.

L. N. K.

Singer, R.: New Observations on the Circulation of the Lower Extremities. I. Arterial Pressure in the Limb Vessels. *Wien. klin. Wchnschr.* 49: 44, 1936.

Changing from lying to sitting or standing position elevates the blood pressure in the lower extremity. This is attributed to a hydrostatic pressure change. Simply changing the position of the leg (or arm) leads to similar fluctuations of pressure.

L. N. K.

Apperly, Frank L., and Cary, M. Katharine: Arterial Hypertension. The Site and Significance of the High Chloride Content of the Blood. *Am. J. M. Sc.* 194: 352, 1937.

In a study to determine the site of increased blood chloride in patients with arterial hypertension, and if possible its significance, it was found:

1. The increased blood chloride is wholly confined to the red cells.
2. This increased cell chloride is not the result of acidemia, since pH and erythrocytic volume-index showed no significant deviations from the normal.

AUTHOR.

Zetter: The Action of Drugs Upon the Permeability of Arteries. *Arch. f. exper. Path. u. Pharmacol.* 185: 141, 1937.

Estimations of the permeability of carotid arteries of swine and a few human femoral arteries were made by the method of Lange. This method consists of placing a 6 to 10 cm. length of artery, tied at each end to a cannula and connected to a manometer, in a small bath (20 c.c. capacity) at body temperature. The lumen of the artery and the surrounding bath are filled with solutions or suspensions different in nature and the passage of material in or out of the artery observed. The intactness of the arteries, chiefly the absence of minute branches, was insured by discarding those which were permeable to congo red, normal arteries having been shown earlier by Lange to be impermeable to this dye. The influence of the addition of drugs either to the fluid surrounding or contained in arteries upon their permeability to fluorescein and naphthol yellow was then tested. Zetter found that nitrites, and either purine or mercurial diuretics increase, and that calcium and nicotine decrease permeability of the arterial walls. The forcefulness of the conclusions are, however, somewhat vitiated by the fact that quantitative measure-

ments seem not to have been possible even though photometric estimations were made of the content of dyes in the bathing fluids. The author merely gives statements that permeability is slightly or markedly increased or decreased, or unchanged. Changes in diameter of lumen appeared not to be related to changes in permeability.

J. M. S.

Goedel, A.: Primary Sarcoma of the Pulmonary Artery. Frankfurt. Ztschr. f. Path. 49: 1, 1936.

A case is reported in a forty-seven-year-old man, the fifth in the literature, of a sarcoma of the pulmonary artery. All cases were diagnosed postmortem. In this case the tumor masses were in the lumina of the vessels, resembling emboli or thrombi grossly. The diagnosis was apparent on histological examination. Only in two cases was growth apparent outside the vessel wall. Metastases were present in the lungs and right heart cavity.

L. N. K.

Perlow, Samuel, and Bloch, Leon: Impending Gangrene of the Feet Due to Ergotamine Tartrate. J. A. M. A. 109: 27, 1937.

In a case of ergotamine tartrate poisoning with impending gangrene of the feet, an apparently complete cure was brought about by the use of papaverine hydrochloride. The patient had received 3.5 mg. of ergotamine tartrate in divided doses within eleven days. On the last day of this medication there was severe pain in the toes and evidences of arterial insufficiency. Seven hypodermic injections of gr.  $\frac{1}{4}$  of morphine were required in twenty-four hours to afford relief of the pain. There was no pulsation in dorsalis pedis or posterior tibial arteries. A diagnosis of spasm and a possibly beginning occlusion of the arteries of both feet was made. Two days later, he was given gr.  $\frac{1}{2}$  of papaverine hydrochloride intravenously, and gr.  $\frac{1}{2}$  twice the next day, following which the pain was relieved and there was great improvement in the condition of the feet. Arterial pulsations returned. On each of the next two days, gr.  $\frac{1}{2}$  of papaverine hydrochloride was given by mouth. Suction and pressure was used toward the end of the papaverine therapy. Within these several days, all signs and symptoms of occlusion disappeared.

H. M.

Singer, R.: New Observations on the Circulation of the Lower Extremities. II. Normal and Pathological Circulatory Changes in the Limb Veins. Wien. klin. Wchnschr. 49: 366, 1936.

The author determines the emptying ability from the vein as follows: the artery is compressed with the limb horizontal, and it is observed that following lowering of the limb 45° below horizontal the vein fills from above, whereas no filling occurs on returning the limb to the horizontal position following elevation of the limb 45°. The state of the vein wall is determined by stretching the vein after stopping the flow from the capillaries. An abnormal vein rigidity is indicated when the vessel remains elevated. The rate of flow into the vein is determined by the refilling time on release of the peripheral compression point of a stretch of vein emptied between compression points.

L. N. K.

Singer, R.: New Observations on the Circulation of the Lower Extremities. III. Clinical Observations. Wien. klin. Wchnschr. 49: 871, 1936.

The blood pressure in the lower extremity in disease sinks to the level in the upper extremity, especially when there is endarteritis. This blood pressure difference

can be used as an index of therapeutic efficacy. Insufficiency of the right heart and early venous thrombosis are manifested by prolonged emptying time of the vein following elevation of the limb 45° from the horizontal. Normally this value is two to six seconds. The refilling time on return to horizontal (normal value five to twenty seconds) gives an index of the state of arterial flow. A refilling time of fifty seconds is to be taken as of serious moment.

L. N. K.

Rautmann, H.: Roentgenological Studies of the Heart in Athletes. *Med. Welt.* 10: 1097, 1936.

A marked dilation of the heart can occur on overexertion without subjective symptoms or cardiac acceleration. This is a good way of checking for overexertion.

L. N. K.

Parade, G. W.: Heart Disease and Athletics. *Med. Welt.* 10: 1101, 1936.

No limitation was noted in the ability to participate in sports in many patients with valvular disease. In fact, regulated exercise will improve the condition by leading to bradycardia, but lack of care in such activity can lead to heart failure. Only myocardial damage is a contraindication to athletics. Arrhythmias like extrasystoles and auricular fibrillation per se are no contraindication for such activities. A case is cited of a skier who had heart block with dropped beats and who had no ill effects from his activity. Nevertheless, each case should be judged individually.

L. N. K.

Grundig, J.: The Management of Congestive Catarrh and Cardiac Asthma in a Spa. *Balneologie* 3: 354, 1936.

Those subject to cardiac asthma due to left heart failure should not be sent to a spa. However, patients with chronic congestive failure such as occurs in mitral stenosis do well at spas. The use of CO<sub>2</sub> baths, O<sub>2</sub> inhalation, and venesection are recommended as is also nitrites or nitrites and digitalis, sedatives, and narcotics.

L. N. K.

Parade, G. W.: Heart Disturbances Following Cold Baths. *Balneologie* 3: 406, 1936.

Baths of 18 to 20° were used on 50 normal subjects. The following abnormal rhythms were found following the use of the cold bath: one instance of A-V dissociation, several of auricular paroxysmal tachycardia, and sinus arrhythmia (nonphasic).

L. N. K.

Crassusi: Clinical Use of *Adonis Vernalis* (Adonigen). *Deutsche med. Wchnschr.* 62: 1613, 1936.

This acts as a sedative to the ectopic pacemakers of the heart. It was used orally and rectally in 57 cases. The indications are similar to those of digitalis. Twenty to thirty drops of adonigen may be used three times a day or one or two tablets orally or one or two suppositories daily.

L. N. K.

# The American Heart Journal

VOL. 14

NOVEMBER, 1937

No. 5

## Original Communications

### ACUTE AND CHRONIC COMPRESSION OF THE HEART\*

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#### PART I. COMPRESSION OF THE HEART

THE compressed heart produces a distinct clinical entity that deserves recognition. The correct concept of cardiac compression has been hidden by a confusing medical nomenclature. It has been hidden also by an incorrect physiological hypothesis. The treatment of the compressed heart is surgical, but correct diagnosis is a prerequisite to the operation.

The compressed heart is a small quiet organ. It cannot undergo dilatation. It cannot undergo hypertrophy. It is the exact opposite of the dilated hypertrophic heart. The anatomical agent producing the compression prohibits the heart from receiving its normal quota of blood for each systole. In as much as it receives a subnormal quota of blood, it actually pumps out a subnormal quota of blood, and the work load of the heart is reduced. The heart can do nothing about this reduction in work and it is forced to play a passive rôle in pumping what blood it receives. I believe that the heart can and actually does undergo atrophy of disuse in the compression diseases. It undergoes disuse atrophy much as any other muscle undergoes disuse atrophy when its work is reduced. After the compression agent has been removed by operation, the heart, like skeletal muscle, requires time to regain its normal strength. Indeed, in chronic cases the compression agent is sometimes removed completely with little improvement in the circulation noticeable after operation. The venous pressure may remain elevated and diuresis may not take place for days or weeks after operation. This delay in recovery I believe is due to the disuse atrophy suffered by the heart.

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Aided by a grant from the Josiah Macy, Jr. Foundation.

Presented at the meeting of the American Heart Association, Section for the Study of the Cardiac Diseases, at Atlantic City, June 8, 1937.

The compressed heart does not waste any of its energy as do many of the dilated, hypertrophic hearts. It functions efficiently although it is not allowed to function adequately. The cardiac valves in the compression diseases are normal. There are no murmurs. The only way in which the valves can become involved is for the insufficiency or stenosis to develop independently of the compression. The efficient, although inadequate, action of the heart is an important point in diagnosis. As the compression develops, the systolic-diastolic excursion of the heart is reduced. Sometimes no trace of pulsation can be seen over the precordium. This observation in itself is sometimes sufficient to enable one to make a differential diagnosis between compression and other forms of failure. It should save the surgeon the embarrassment of operating upon the dilated, hypertrophic, failing heart. Reduction in the amplitude of the heart beat can be seen by fluoroscopic examination. This examination is helpful not only in making the diagnosis of the condition but also in giving the surgeon important information concerning the operation. By it the surgeon sometimes can determine the nature of the compression agent, whether it is fluid, scar tissue, or tumor. He can also determine whether the operative approach should be to the right or to the left of the sternum. A record of the cardiac excursion can be made by the roentgen kymograph film. On the basis of the discussion so far it is clear that the compressed heart should be regarded as a small quiet organ. Cardiac compression has many other points of interest.

Let us now consider the flow of blood from the venae cavae into the heart. Let us consider the pressures exerted upon the venae cavae as they penetrate the pericardial cavity. These pressures under normal conditions are negative or less than the pressure of atmosphere. Now, if the pressure in the pericardial cavity is rapidly increased, as by the collection of blood, the venae cavae and the right auricle are immediately collapsed and the forward movement of blood is brought to a standstill. This condition exists until the pressure within the venous system builds itself up to a level high enough to break through the intrapericardial barrier. Blood then enters the heart. A delicate play of pressures exists between intrapericardial pressure and intravenous pressure. When the former increases, the latter must increase. Otherwise the patient dies. The pressure upon the intrapericardial structures can go up to certain definite levels. These levels are determined only by the heights to which the venous pressure can rise. The compression force upon the heart can never remain at a higher level than the pressure in the venae cavae. This statement can be considered as a physiological law. When the heart is acutely compressed, as occurs when a myocardial infarct or contusion ruptures, the venous pressure cannot rise above 15 or 20 cm. of water, and this is the fatal level in all cases of acute compression.

A pressure differential, so necessary to life, can be reestablished in two ways. One is to raise the venous pressure, the other is to reduce the compression. The venous pressure can be elevated to new high levels by the addition of fluid to the venous system. This point is of practical importance and may be applied in patients bleeding from the heart while preparation for operation is being made. In experiments in which a fatal compression level has been reached, the venous pressure can be promptly elevated to 25 or 30 cm. by the intravenous injection of fluid. In such experiments the arterial pulse returns and life can be prolonged.

The other signs and symptoms of acute cardiac compression are obvious. The veins are filled with blood. The venous pressure rises to 15 or 20 cm. The liver has not had time to enlarge. For the same reason ascites and subcutaneous edema are not present. The arterial circulation is weak and the arterial pressure falls. The mental anguish, excitement, or unconsciousness comes from cerebral anoxemia. The skin grows cool and moist.

*Chronic compression* of the heart produces a different picture. I produced chronic compression by the introduction of Dakin's solution into the pericardial cavity.<sup>1, 2</sup> This chemical irritant sometimes brought about a slowly forming accumulation of bloody fluid in the pericardial cavity without adhesions and produced the clinical picture of chronic compression. Sometimes the Dakin's solution brought about scar tissue formation on the epicardium and in the pericardium which in turn underwent contraction and compressed the heart. Experimentally it was found that the heart could tolerate a higher degree of compression if the compression developed slowly than if it developed acutely. In human patients the compression force may rise to remarkable levels.<sup>3</sup> In my series of patients the greatest compression force was from 40 to 45 cm. of water. It is interesting to speculate concerning the adaptation that makes such high compression forces possible. Why will a compression of 15 to 20 cm. kill when applied acutely, and why can 40 to 45 cm. be tolerated in the chronic conditions? The explanation lies in the venous pressure levels. There is not sufficient blood in the vascular system to elevate venous pressure above 15 to 20 cm. in response to acute compression. In the chronic condition we have some evidence to show that an increase in the circulating blood volume takes place.\* Another possible cause in the elevation of venous pressure is brought about by the accumulation of fluid that slowly forms in the tissues and serous cavities. This fluid compresses the peripheral vascular tree to some extent and elevates the venous pressure.

\*Some of these measurements were made on experimental animals, others on patients with compression. The data are not complete and are not to be considered as final because we have been having difficulty in obtaining satisfactory admixture of dye with the slowly moving blood. Also the presence of bile pigments in the blood in cases of chronic compression is a source of error in making colorimetric determinations.

The clinical manifestations of chronic compression of the heart are produced by venous stasis and a reduced arterial circulation. The veins are distended and sometimes elongated. They may stand out like goose quills. Cyanosis, ascites, enlargement of the liver and spleen, subcutaneous edema, varicose veins, hemorrhoids, hydrothorax, and pulmonary edema are all expressions of venous stasis. The liver becomes cirrhotic in response to long continued circulatory stasis. The liver and spleen may be coated with a fibrinous or fibrous exudate and the peritoneum may be thickened. These alterations in the abdomen are not infectious in origin nor are they tuberculous, as was formerly thought. They were present in our experiments and are due to venous stasis. Weakness, loss of subcutaneous fat, and retardation of growth are due to a reduction in arterial blood flow. Pulsus paradoxus is frequently present. The systolic pressure is usually 100 and the diastolic 80 mm. of mercury. The pulse pressure is about 20 mm. of mercury. Fixation of the heart to the sternum or to other structures has no diagnostic or therapeutic significance. Low voltage and slurring of the QRS complex are usually seen in the electrocardiogram. Fixation of electrical axis may or may not be present.

The diagnosis of cardiac compression should not be difficult. I have assembled two triads that should be helpful in the diagnosis of these conditions. The triad for acute compression of the heart (Fig. 1) is (1) a small quiet heart, (2) a rising venous pressure, and (3) a falling arterial pressure. The triad for chronic compression of the heart (Fig. 2) is (1) a small quiet heart, (2) a high venous pressure, and (3) ascites and enlargement of the liver. These triads cannot be wrong. Difficulties come in recognizing the small quiet heart. To some clinicians the small quiet heart is an unknown concept.

There are two reasons for this obscurity. One is the confusing medical nomenclature. Such terms as adhesive pericarditis, constrictive pericarditis, chronic oblitative pericarditis, concretio pericardii, symphysis cordis, pericarditic pseudocirrhosis of the liver, mediastino-pericarditis, Pick's disease, Concato's disease, and polyserositis are confusing. To quote from one of our text books: "This form of chronic peritonitis may be a part of a polyserositis (Concato's disease) and is especially often associated with chronic indurative mediastinopericarditis, of which Pick's pericardial pseudocirrhosis is a part. . . . The physical signs are those of ascites. . . . The coincidence of the signs of ascites with chronic oblitative pericarditis or with arteriolar nephropathy help in making the diagnosis." Such medical verbiage is confusing and should be dropped from our present-day text books of medicine.

The other cause for confusion lies in the general acceptance of an incorrect physiological hypothesis, namely, the belief that adhesions to the heart play a rôle in producing failure, dilatation, and hypertrophy of the heart. I feel secure in stating that adhesions to the heart do

not produce dilatation, failure, or hypertrophy of the heart. Adhesions play no part in the production of the compression syndromes. When present, adhesions are silent and incidental findings and produce no circulatory trouble whatsoever unless the heart is acutely angulated or twisted. Our experimental and clinical evidence for these statements is conclusive and leaves no room for doubt.

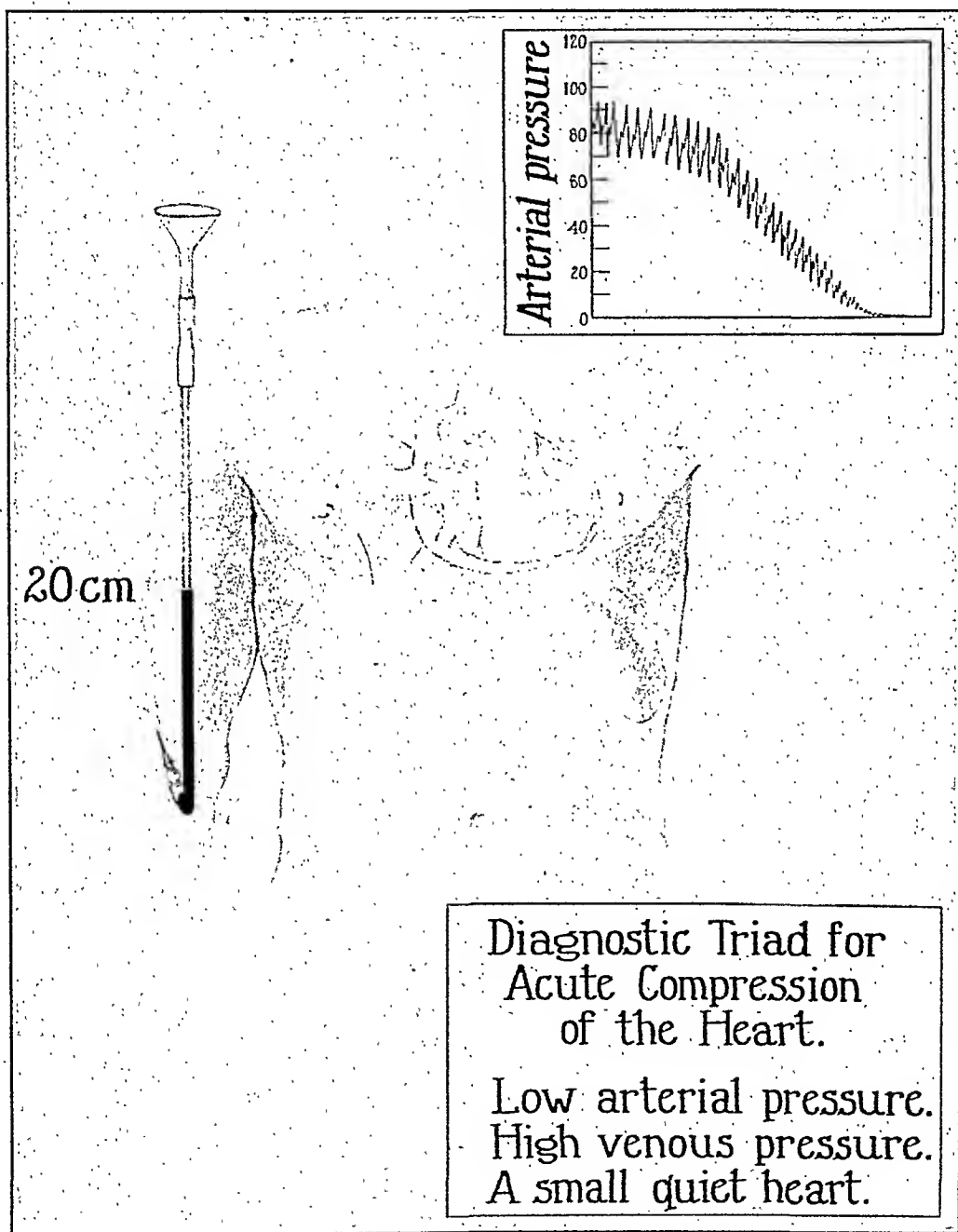


Fig. 1.—Acute compression of the heart. Note collapse of venae cavae and left auricle. The ventricles are smaller than normal because the heart contains a sub-normal quantity of blood.

If our discussion is correct, this group of disorders no longer remains vague and intangible. The compressed heart becomes something definite both physiologically and clinically. It is just as definite as is a compressed brain. We are acquainted with the choked disc, headache, and



vomiting of a compressed brain. We should be equally well acquainted with the small, quiet, compressed heart. If our discussion on compression is acceptable, not only does the clinical picture become definite, but also the clinician is brought straightway to a consideration of the nature of the agent producing the compression, and, after the pathology of

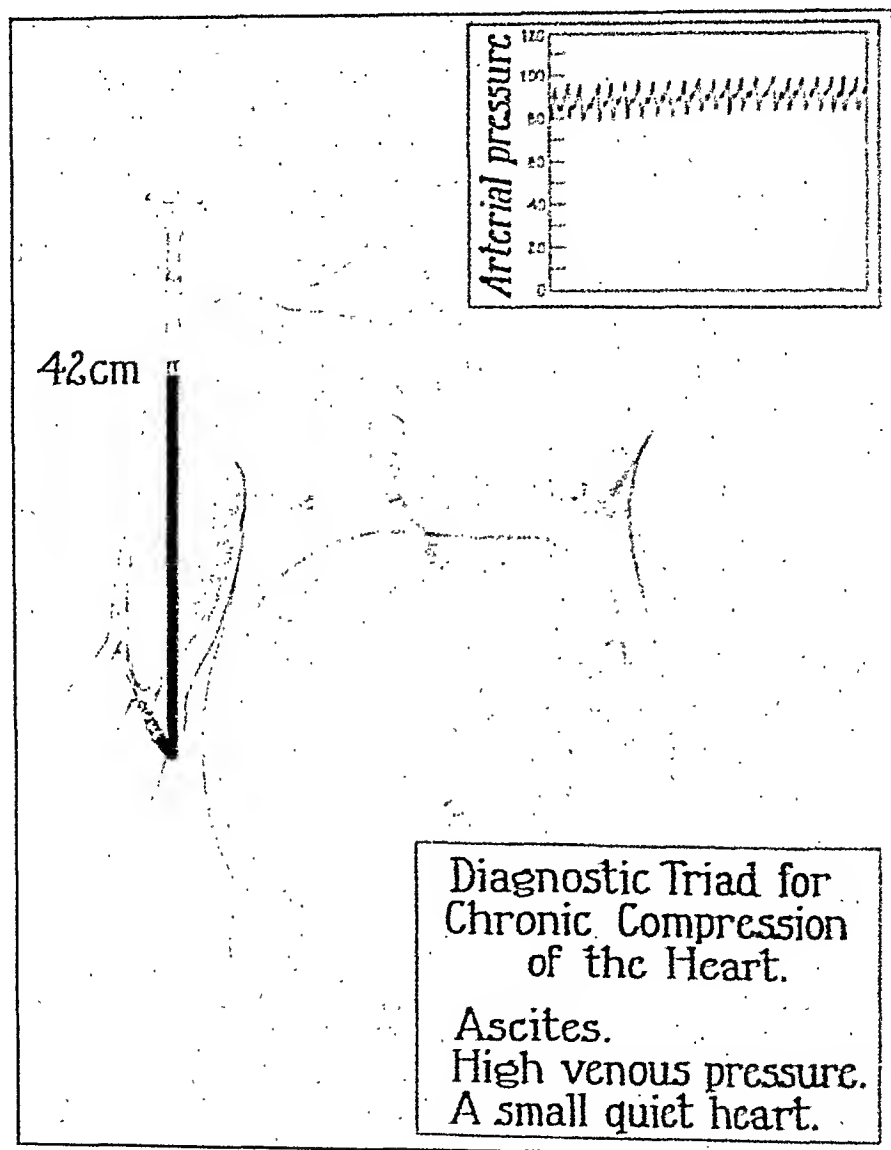


Fig. 2.—Chronic compression of the heart. The cardiopericardial silhouette must be differentiated from that of the heart alone. The heart is a small shrunken organ that undergoes disuse atrophy.

the lesion has been determined—and only after this has been determined—the proper treatment can be given.

Acute compression of the heart is always produced by a fluid. The fluid is usually blood but it can be a sterile exudate or pus. Only two types of acute cardiac compression have received surgical treatment.

The penetrating wound of the heart has been treated surgically, as has also the compression from pus in the pericardial cavity. So-called spontaneous rupture of auricles or ventricles has not been given the benefit of operation. Similarly acute compression produced by hemorrhage from a myocardial contusion or from a myocardial infarct has not been treated surgically. I can say with assurance that some of these are examples of neglect. Because some of these lesions have not been operated upon in the past is no adequate reason why they should not be operated upon in the future. The literature contains examples of slow hemorrhage, slow in terms of time required for getting ready to do the operation. The lesion responsible for the bleeding is not always extensive. Some of the lesions are amenable to suture or to reinforcement by a graft of pericardium. I feel confident that in the future a development will take place by which a larger proportion of these cases of acute compression will be treated by operation.

Chronic compression of the heart is produced by a variety of anatomical lesions. The compression agent may be fluid, scar tissue, neoplasm, or a combination of several of these lesions. The fluid may be sterile or infected. Hemorrhage from the heart may produce chronic compression, the bleeding being slow or intermittent. I had one patient with a sarcoma of the heart. The tumor bled intermittently and produced compression. Slow hemorrhage into the mediastinal cavity following the removal of a substernal goiter is known to have produced compression. Mediastinal effusions may produce compression. I have had a number of such effusions following operation on the heart. This complication is now cared for by establishing internal drainage into the pleural cavity at the time of operation. Some of the compressions are due to infections followed by the formation and contracture of scar tissue. The infection may be insidious and the development of the compression signs may be gradual and after they develop the patient may complain only of ascites and weakness. An extensive deposit of calcium may be laid down in the scar. In most of my cases of compression scars the nature of the organism could not be determined. Most of them, I believe, were pyogenic and only about 10 per cent were proved to be tuberculous. The chronic effusions may be tuberculous; from some of them no organisms can be recovered. One of my patients had mild compression signs from a non acid-fast tuberculous abscess lying over and compressing the venae cavae and right auricle. Two of my patients had compression from an invasion of parietal pericardium and mediastinum by sarcoma. In these patients the pericardium was thickened but not adherent to the heart. Another patient had a thickened parietal pericardium, bloody pericardial fluid, and an epicardial scar. In this case three factors were responsible in producing compression: the parietal pericardium was too thick to stretch; the fluid aided in the compression, and the epicardial scar had to be removed because it also

compressed the heart. The heart can be compressed or partially strangulated through a traumatic rupture of the parietal pericardium. The compression scars may be localized or generalized over the entire heart. The venae cavae and right auricle were compressed in some of our experiments. I have seen one specimen in which a band of calcified scar surrounded the two ventricles, there being no other involvement. In another patient a calcified ring of tissue surrounded the pulmonary artery.

The experiences obtained in the treatment of these conditions cannot be presented in this paper. It is needless for me to say that many of these patients with chronic cardiac compression can be cured by operation and the cures are permanent. The question has been raised as to whether adhesions form again after resection of a scar from the heart. Adhesions do form, but again may I add that adhesions play no part in the production of compression. If the infection has become quiescent before operation, if it has burned itself out so to speak, a thick scar which later undergoes contracture will not form again and the cure is permanent.

#### PART II. ADHESIONS TO THE HEART

Since the time of Auenbrugger, Corvisart, and Laënnec, we have been laboring in the dark concerning the subject of adhesions to the heart. It is generally believed that adhesions disturb the heart action and that they can produce dilatation, hypertrophy, and failure. The relationship between adhesions, on the one hand, and dilatation, hypertrophy, and failure of the heart, on the other hand, has been generally considered as one of cause and effect. Because of a belief in this causal relationship, medical men have been chagrined when they have not recognized adhesions in cases of failure. These diagnostic mistakes or omissions in cases of adhesions are not infrequent. As an aid in diagnosis Norris and Landis wrote as follows: "Whether cardiac murmurs are present or not, adhesive pericarditis is to be thought of in a young adult if there is a history of acute rheumatic fever followed by endocarditis, and, especially so if the cardiac failure is more marked or the cardiac enlargement more extensive than the endocardial damage seems to warrant. An additional point of some importance is the fact that in young individuals apparently suffering from endocarditis, an adherent pericardium is to be suspected when the heart does not respond to digitalis." Much has been written on the diagnosis of adhesive pericarditis. Retraction of the chest wall, Broadbent's sign, friction rubs, and fixation of the electrical axis are all supposed to mean something in the way of diagnosis. There are many signs described for the diagnosis of pericardial diseases. The clinician has even listened for and heard the "pericardial knock." In

spite of all these diagnostic endeavors, why is it that the diagnosis of adhesive pericarditis is little more accurate than a guess? The answer, although fundamental, is simple.

From 1923 to the present time I have continuously had in progress some type of recovery experiment on the heart and pericardium. Regardless of the purpose of these experimental studies, adhesions to one or more of the structures adjacent to the heart were encountered in practically every experiment. In 1931 I reported the results of a special study of intrapericardial and extrapericardial adhesions produced experimentally.<sup>4</sup> The conclusions arrived at were that such adhesions did not produce circulatory embarrassment, that they did not produce hypertrophy, dilatation, or failure of the heart. During the past six years we have been deliberately grafting tissues upon the heart for the purpose of producing a new blood supply to the myocardium.<sup>5</sup> The tissues grafted upon the heart were parietal pericardium, mediastinal fat, pedicle grafts of muscle from the chest wall, and omentum. In all I would estimate that well over a thousand experiments on the heart have been carried out. Again on the basis of this experience it was my impression that adhesions produced little or no disturbance to the heart. Acute angulation or torsion of the heart on its long axis did disturb the heart and produced changes in arterial and venous pressures, but the ordinary pull upon chest wall or diaphragm was well tolerated. In 1933 Hosler and Williams<sup>6</sup> began a series of carefully controlled experiments for the purpose of making more accurate measurements on this subject. They divided their experiments into three groups: (1) extrapericardial, i.e., adhesions between parietal pericardium and diaphragm; (2) intrapericardial, or adhesions between parietal pericardium and heart; and (3) combined, in which heart, pericardium and diaphragm were united. In one of these experiments the pull was so great as to produce a sacculation or diverticulum of the right ventricular cavity. The animals were exercised upon a tread mill and were observed over a period of two years. Cardiac hypertrophy was not found in any of these experiments either grossly or microscopically. Likewise failure and dilatation were not found. Hosler analyzed the autopsy material at the University Hospitals and found 75 instances of extensive pericardial adhesions in 4,400 autopsies. This group of 75 was divided into 54 in which hypertrophy was present and 21 in which hypertrophy was absent. In each of the 54 cases there was concomitant heart disease or vascular disease which in itself could account for the hypertrophy. Almost without exception the largest hearts were the seat of rheumatic pancarditis. An analysis of the 21 hearts with extensive adhesions but without hypertrophy showed that these hearts were free from valvular, myocardial, or vascular disease in all except one case and this showed mild rheumatic heart disease. I believe that we can be positive in

asserting that adhesions to the heart do not produce dilatation of the heart, failure of the heart, or hypertrophy of the heart. The only way in which adhesions can impair the circulation is by producing acute angulation of the heart from its normal axis or by producing torsion of the heart either clockwise or counterclockwise in the long axis of the heart. Such acute dislocations of the heart are readily produced when the heart is exposed at operation. They are rarely encountered in patients.

The exact mechanism by which angulation and torsion of the heart disturb the circulation needs further study. It is our opinion that the great vessels at the base of the heart are primarily involved. However, neurogenic disturbances resulting in changes in heart rate seem to be possible as demonstrated by a patient whom we now have under observation. It should be pointed out that angulation and torsion of the heart interfere with the circulation in a manner entirely different from energy-loss by pulling upon chest wall or diaphragm.

On the assumption that the heart wastes energy in pulling upon chest wall through adhesions, attempts have been made to correct this condition by operation. Let us assume that the heart has become adherent to parietal pericardium and that the pericardium has become adherent to the chest wall.\* As the heart beats, the chest wall is pulled upon and this movement appears to be a waste of energy. When the heart begins to increase in size as it frequently does in those conditions in which adhesions appear (rheumatic heart disease) the waste of energy is considered as a cause of the hypertrophy and enlargement. On this assumption the next step is towards correction. Two possibilities exist. One is to sever the central end of the adhesion, i.e., the heart end. The other is to relax the particular part of the chest wall that is pulled upon by removing the ribs from this particular area. The first alternative has never been utilized, but in 1902 the second idea was applied and the Brauer<sup>8</sup> operation came into being. This operation has been reported in over a hundred cases and is incorrectly called a "cardiolysis."

What results have been obtained by this operation?<sup>9</sup> In analyzing the results I am reminded of a patient whom I saw about five years ago. He had panrheumatic heart disease with adhesions. He was critically ill with ascites, hydrothorax, cyanosis, etc., and any type of operation was out of the question. He was sent home to die. Today this patient is remarkably well and all signs of failure have disappeared. He leads an active life. If the operation had been done and if he had survived it, it would be considered that an excellent result had been obtained from

\*Broadbent<sup>7</sup> noticed that even if the heart were not directly adherent to the chest wall a pull upon the chest wall, nevertheless, could be effected by pulling upon the diaphragm.

the Brauer operation. The results of the operation in general cannot be analyzed with any degree of accuracy. There is no similar control group for comparison. If I might express an opinion, I would say that the extra bed rest and attention afforded these patients before and after operation did them more good than the operation itself. Even this statement implies that the operation did some good and of this I am skeptical.

In conclusion, I believe that adhesions to the heart are silent and incidental, that there may be no reason for their recognition clinically, and that there is no reason to operate for their correction.

#### REFERENCES

1. Beck, C. S.: The Effect of Surgical Solution of Chlorinated Soda (Dakin's Solution) in the Pericardial Cavity, *Arch. Surg.* 18: 1659, 1929.
2. Beck, C. S., and Griswold, R. A.: Pericardiectomy in the Treatment of the Pick Syndrome; Experimental and Clinical Observations, *Arch. Surg.* 21: 1064, 1930.
3. Beck, C. S., and Cushing, E. H.: Circulatory Stasis of Intrapericardial Origin; the Clinical and Surgical Aspects of the Pick Syndrome, *J. A. M. A.* 102: 1543, 1934.
4. Beck, C. S.: The Surgical Treatment of Pericardial Scar, *J. A. M. A.* 97: 824, 1931.
5. Beck, C. S., and Tichy, V. L.: The Production of a Collateral Circulation to the Heart; I. An Experimental Study, *AM. HEART J.* 10: 849, 1935.
6. Hosler, R. M., and Williams, J. E.: A Study of Cardiopericardial Adhesions, *J. Thoracic Surg.* 5: 629, 1936.
7. Broadbent, Sir W.: An Unpublished Physical Sign, *Lancet* 2: 200, 1895.
8. Brauer, L.: Ueber chronische adhäsive Mediastino-Perikarditis und deren Behandlung, *München. med. Wehnschr.* 49: 1072, 1902.
9. Smith, E. S., and Liggett, H. S.: Cardiolytic for Chronic Mediastino-Pericarditis, *Proc. Internat. Assemb. Inter-State Post-Grad. M. A., North America* (1928), pp. 489-502, 1929.

## THE USE OF MERCUPURIN IN THE TREATMENT OF CONGESTIVE HEART FAILURE AND IN THE MOBILIZATION OF EXCESS BODY FLUID\*

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WE ARE so frequently confronted with manifestations of congestive heart failure that methods of combating them are a matter of great concern. That the methods are *at times* and indeed *finally* unsuccessful is ample evidence that we have not yet found the infallible diuretic. It is important therefore for us to test rigidly and impartially any new diuretic drug that gives promise of being beneficial.

In heart failure of the congestive type, and in certain other unrelated conditions in which there is accumulation of excess fluid in the body, such as cirrhosis of the liver exhibiting ascites, reduction in the amount of excess fluid is commonly followed by relief of symptoms. This beneficial effect is often attained by the administration of drugs possessing diuretic action. Since the introduction of salyrgan by Bernheim in 1924,<sup>1</sup> this organic mercurial diuretic has been widely used in the treatment of heart failure of the congestive type and cirrhosis of the liver exhibiting ascites; it is now recognized to be a potent drug of low toxicity.

In an attempt to make an even more potent and less toxic diuretic than salyrgan, von Issekutz and von Végh<sup>2</sup> in 1928 described a new organic mercurial diuretic which they called novurit. Novurit differed from salyrgan in two respects: first, the mercury containing radical was a different organic substance; and second, it contained theophyllin, which was said to be chemically bound to the mercurial compound. Von Issekutz and von Végh claimed that the diuretic effect of novurit in rabbits was considerably greater than that of salyrgan and also that it was only one-half as toxic in rats. Since the introduction of novurit it has been shown by Herrmann, Schwab, Stone, and Marr,<sup>3</sup> that the combination of theophyllin and a mercurial diuretic exerts a diuretic action greater than that of either of the drugs when given alone. Furthermore, DeGraff and Batterman<sup>4</sup> have observed that the presence of theophyllin at the site of injection of mercurial diuretics tends to prevent the local toxic effects of the mercurial drug on the tissues. In the light of these observations a drug containing theophyllin in chemical combination with a mercurial compound might possess certain advantages not inherent in or possessed by salyrgan.

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Novurit is said to contain mercury 0.0393 gm. per cubic centimeter, an amount approximately identical with that in salyrgan. In addition, it contains 5 per cent of theophyllin, 3.5 per cent of which is said to be chemically bound to the organic mercury compound. During the past two or three years novurit has been sold in the United States under the proprietary name "mercupurin."<sup>\*</sup> Novurit and mercupurin are names for the same substance.

Clinical experience with mereupurin has been recorded within the past seven years by Hahn,<sup>5</sup> Popper,<sup>6, 7</sup> Saxl,<sup>8</sup> Spengler,<sup>9</sup> Engel and Epstein,<sup>10</sup> and Pratsicas,<sup>11</sup> abroad, and within the past two years by Crawford and McDaniel,<sup>12</sup> Fulton and Bryan,<sup>13</sup> Steuer and Wolpaw,<sup>14</sup> and DeGraff, Nadler, and Batterman<sup>15</sup> in the United States. The number of patients to whom these investigators gave mereupurin varied from three to sixty. Most of the patients were suffering from heart failure of the congestive type, a few from cirrhosis of the liver exhibiting ascites. None of these investigators gave more than a few injections to each patient. Toxic effects were not observed. Certain observers<sup>8, 9, 10, 13, 14</sup> were of the opinion that it was as satisfactory as salyrgan, while others<sup>5, 6, 7, 11, 12, 15</sup> found it more effective. In addition to the papers already quoted, there are many in the Slavic languages which were not available to us.

The effects of the administration of mercupurin to patients on the medical pavilions of the New York Hospital have been observed for one year. No effort was made to study the mechanism of action of mercupurin nor to compare directly the effect of mercupurin and that of salyrgan. The results of these observations under conditions similar to those in which the drug is commonly used form the subject of this report.

#### METHODS OF OBSERVATION

All patients were at rest in bed. With a few exceptions a diet containing two grams of salt was given. The intake of fluid was restricted to 1,200 c.c. a day in most instances. Occasionally a larger amount was given, usually because fever was present. Many of the patients suffering from heart failure of the congestive type received maintenance doses of digitalis daily and many of them were given theocaine, theobromine sodiosalicylate, or aminophylline as well. The data forming the basis for this report comprise only those observations in which the diuretic effect of mercupurin could be isolated from the effects of other drugs if they were being given. Most patients received ammonium chloride, 3.0 gm. daily, at the same time. Patients were weighed daily before breakfast unless they were so ill that it appeared advisable to weigh them at intervals of several days instead. The intake of fluid and

<sup>\*</sup>We have used in our studies mercupurin prepared by Campbell Products Inc., New York City.



output of urine were measured in twenty-four-hour periods. Since the apparent diuretic effect was the same whether the volume of urine or the loss of weight was selected as the criterion, the former, namely the volume of urine, was used as the measure of diuresis.

With the exception of one patient, Mrs. M. L., Case No. 4, who received the drug intramuscularly, it was given intravenously without dilution. It was given in the morning in order that the volume of urine excreted on the day of injection might represent the largest part of the diuretic effect. In most instances a trial dose of 1.0 c.c. was given, and followed after an interval of twenty-four hours by the usual therapeutic amount, 2.0 c.c. This amount was repeated at three-day intervals as long as there was indication for its use. The interval became longer as the accumulations of fluid decreased. The use of the drug was continued until improvement reached a satisfactory stage or until it failed to induce diuresis. In certain cases it was given at irregular intervals as it appeared to be indicated.

#### OBSERVATIONS

Four hundred thirty-eight injections were given to 66 patients presenting clinical evidence of accumulation of fluid in the tissues. Fifty-two of these exhibited heart failure of the congestive type. In them the etiology of the heart disease was rheumatic fever in 19 (Cases No. 1 to 16 inclusive, 59, 60, 61), arteriosclerosis in 13 (Cases No. 17 to 25 inclusive, 62-65), hypertension in 10 (Cases No. 26 to 35 inclusive), syphilis in 2 (Cases No. 36 and 37), pericardial disease in 6 (of these, 5 [Cases No. 38, 40-43] suffered from chronic constrictive pericarditis and 1 [Case No. 39] from recurrent pericardial effusion), and pulmonary fibrosis\* in 2 (Cases No. 44 and 45). Nine patients (Cases No. 46 to 53 inclusive and 66) suffered from cirrhosis of the liver exhibiting ascites. Of the five patients remaining, 2 (Cases No. 54 and 55) exhibited the nephrotic stage of chronic glomerular nephritis, 1 (Case No. 56) hydrothorax and ascites of unknown etiology, another (Case No. 57) ascites as a consequence of tuberculosis of the peritoneum; and finally 1 (Case No. 58) exhibited hydrothorax and ascites secondary to carcinomatosis of the pleura and peritoneum respectively.

Patients received from 1 to 45 injections: forty-one received from 1 to 5 injections; twelve, from 6 to 10; seven, from 11 to 15; and three, from 16 to 20. Mrs. C. K., Case No. 46, received 29 injections in six months. Another patient, Mrs. A. R., Case No. 38, received 36 injections in twelve months, while another, Miss E. C., Case No. 39, received 45 injections in thirteen months. These two, as well as four others, were given mereupurin in the out-patient department after discharge from

\*Pulmonary fibrosis was considered to be the etiological factor in those cases in which there was observed pulmonary emphysema, enlargement of the right ventricle, cyanosis out of proportion to the other evidences of heart failure, and lack of evidence of any one of the other more usual etiological factors.

the hospital. Evaluation of the effect of injections given in the out-patient department was made from a consideration of the occurrence of systemic toxic effects, of undesirable reactions at the site of injection, of the apparent effectiveness of the drug in preventing the reaccumulation of fluid, of a statement of the patient as to the diuretic effect, and finally in certain instances, of measurement by the patient of the volume of urine. The results of the injections given to patients in the out-patient department are not, however, included in the quantitative data recorded in Figs. 1 and 2, which form the basis for our analysis of the effectiveness of this drug.

Only 286 of the 438 injections appear to represent the diuretic effect of mercupurin uninfluenced by factors which might have altered the result obtained from the drug. That is to say, the results from 152 injections were discarded either because of incomplete data, or because the simultaneous administration of another drug did not permit us to

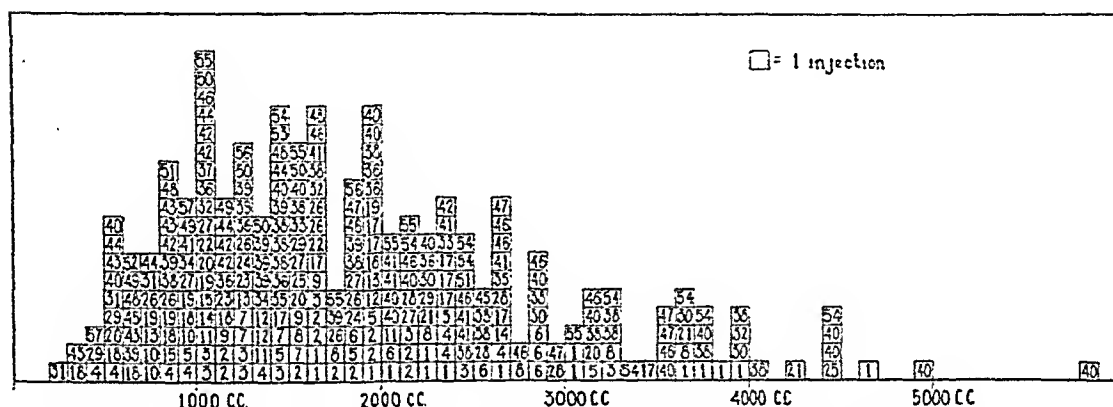


Fig. 1.—This figure represents a frequency distribution of the daily amounts of urine from 200 c.c. to 6,000 c.c. in 100 c.c. increments resulting from 286 injections of mercupurin in 57 patients. Each square represents 1 unit, that is to say, 1 injection. The numbers in the squares identify the patients. In patients numbers 1 to 16 inclusive and 59, 60, 61, the etiological diagnosis was rheumatic fever; in numbers 17 to 25 inclusive and 62-65, arteriosclerosis; in numbers 26 to 35 inclusive, hypertension; in numbers 36 and 37, syphilis; in numbers 38 to 43 inclusive, pericardial disease; in numbers 44 and 45, pulmonary fibrosis; in numbers 46 to 53 inclusive and 66, cirrhosis of the liver exhibiting ascites; in numbers 54 and 55, the nephrotic stage of chronic glomerular nephritis; in number 56, hydrothorax and ascites of unknown etiology; in number 57, ascites as a consequence of tuberculosis of the peritoneum; and in number 58, hydrothorax and ascites secondary to carcinomatosis of the pleura and peritoneum respectively.

make an estimate of the effect of mercupurin. The 286 injections which satisfy our criteria were given to 57 patients.

#### DISCUSSION OF RESULTS

Statistical analysis of the data relating to the 286 injections which satisfy our criteria yields more information about the results to be expected from giving mercupurin than can be obtained by the study of individual cases. For this analysis data have been arranged in the form of two frequency curves (Figs. 1 and 2). The general trends of diuretic effect appear from examination of each chart as a whole and the analysis of each as a frequency curve. From these curves also may

be observed the variation in effect in individual cases, as well as the influence of etiology on the diuretic effect.

For instance, it appears that the diuretic effect in the greatest number of the injections lies in the zone representing a diuresis of between 1,000 and 2,000 c.c. in twenty-four hours (Fig. 1). The output of urine on the day of injection, however, varied between extremes of 200 and 300 c.c. and 5,800 and 5,900 c.c. The following facts stand out: on one occasion only was a diuresis greater than 5,000 c.c. obtained: 8 injections given to 6 patients resulted in a diuresis of between 4,000 and 5,000 c.c., while 33 injections given to 15 patients yielded an output of urine of between 3,000 and 4,000 c.c., and 69 injections given to 28 patients gave a diuresis of between 2,000 and 3,000 c.c. A volume of urine less than 1,000 c.c. occurred with relative infrequency.

Analysis was made from another point of view: it appears that the most frequent effect of the drug was to increase the volume of urine on the day of injection from two to five times over that on the preceding day (Fig. 2); the extremes show at one end that the output of urine on the day of injection was occasionally less than the amount on the preceding day, and at the other end that it was 19 times that amount. It was uncommon for the urinary output to increase 10 times or more. Increases of from 5 to 10 times were observed in relatively few instances. Only 24 of 286 injections failed to produce any increase in the urinary output. From the distribution of numerals referring to patients in Figs. 1 and 2, it is apparent that in certain patients an injection might at one time produce marked diuresis and at another time be less effective. For example, Case No. 38 gave a number of responses of between 1,000 and 2,000 c.c., and also a number which lay between 3,000 and 4,000 c.c. In certain instances the variation in response appeared to be related to the amount of excess fluid present: in others it was not possible to attribute the difference in effect to this cause and we were unable to account for it. In other patients small diuretic responses were usually obtained, as for example Case No. 18, whose response was usually less than 1,000 c.c. In other patients, still, consistently good effects were obtained; for example, in Case No. 40 the diuresis was usually in excess of 3,000 c.c.

These data have been analyzed also with respect to the bearing of etiology on the effectiveness of this diuretic drug (Figs. 1 and 2). Five cases of chronic constrictive pericarditis (Cases No. 38, 40-43) as an etiological group, showed the best diuretic effect. There did not appear to be any significant difference in effect between cases of heart failure of the congestive type whether it was of rheumatic, of arteriosclerotic, or of hypertensive etiology. Nine cases of cirrhosis of the liver exhibiting ascites, as a group, showed smaller effects than any of the other etiological groups in which the number of cases was comparable; nevertheless, excellent diuresis was occasionally obtained in this group. For

example, Mrs. C. K., Case No. 46 (Fig. 7) usually responded to an injection by a urinary output of over 2,500 c.c. so that the drug was quite effective in preventing the recurrence of ascites. With respect to

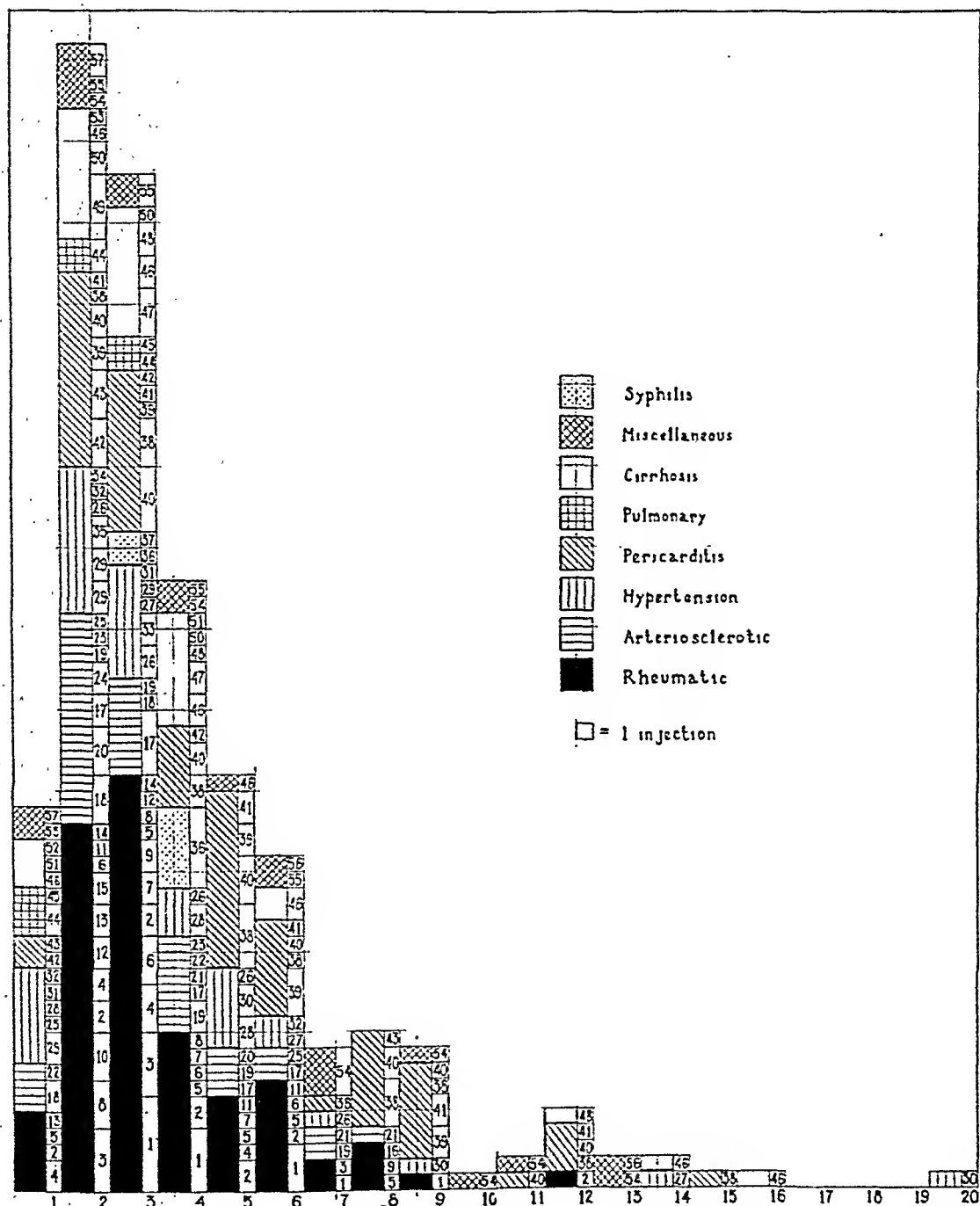


Fig. 2.—This figure represents a frequency distribution of the quantitative diuretic effect of mercupurin, calculated on the ratio of the urine output on the day of the injection to the day before injection. In it are recorded 286 injections given to 57 patients. The unit is one injection. The numbers, which are the same as in Fig. 1, are used to identify the patients. In the column parallel to the units in each quantitative rubric are placed symbols indicating the etiological diagnosis. In each column the same sequence of etiological classification is maintained.

the other etiological groups, namely syphilitic heart disease, pulmonary heart disease, and the miscellaneous group of 6 cases, the number of patients was too small to permit a general statement.

The diuretic effect of mercurpurin is recorded in data secured from 5 patients illustrating as many etiological groups (Figs. 3 to 7).

In the case of Mr. J. H., Case No. 1, a white male, forty-eight years of age, the diagnoses\* were: (a) rheumatic fever; (b) cardiac enlargement, mitral stenosis and insufficiency; (c) auricular fibrillation, and heart failure of the congestive type. He had suffered from dyspnea and ankle edema for twelve years before admission. He exhibited the following signs of heart failure: many moist râles at the bases of both lungs posteriorly, marked swelling of the liver, a small amount of fluid in the peritoneal cavity, and massive pitting edema of the lower legs and thighs. It was found that rest in bed and the administration of digitalis had little diuretic effect. Because auricular fibrillation was present, the use of digitalis was, however,

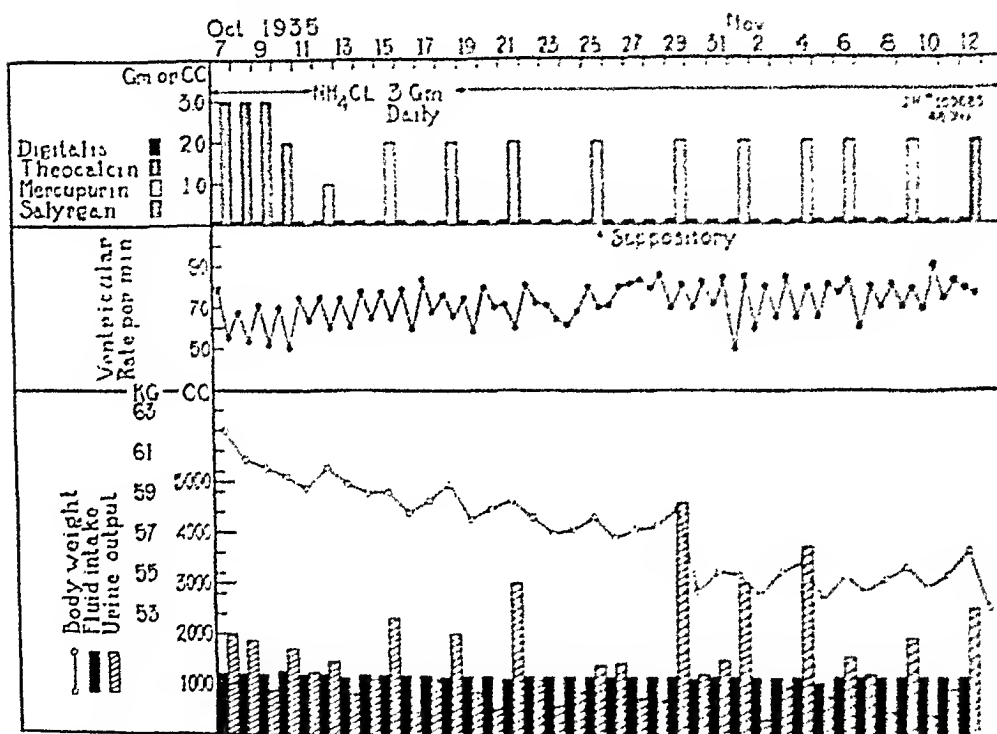


Fig. 3.—In this figure is represented the diuretic effect of mercurpurin in the case of J. H., Case No. 1, suffering from rheumatic heart disease.

continued. On giving mercurpurin, excellent diuresis, attaining 4,600 cc. a day, was obtained (Fig. 3), associated with loss in body weight and the regression of the physical signs of heart failure.

Mr. W. W., Case No. 21, a white male, sixty-eight years of age, suffered from arteriosclerotic heart disease. The diagnoses were: (a) arteriosclerosis; (b) enlargement of the heart; (c) auricular fibrillation, and heart failure of the congestive type. He had experienced dyspnea, edema of the ankles, and precordial pain both on exertion and at rest for one and one-half years, and orthopnea and cough for two months. The following signs of congestive heart failure were observed: many moist râles at both lungs bases, a small amount of fluid in both pleural cavities, moderate swelling of the liver, and marked pitting edema of the lower legs, thighs, and sacral region. On the exhibition of rest in bed, digitalis, and theobromine sodiosalicylate

\*The cardiac diagnoses in this paper conform to the nomenclature for cardiac diagnosis recommended by the American Heart Association, AM. HEART J., 2: 202, 1926-27.

no demonstrable change in the physical signs occurred. Injections of mercupurin were then given and induced a tremendous increase in the output of urine, which was as great as 4,200 c.e. a day (Fig. 4), accompanied by rapid decrease in the accumulation of fluid.

In the case of Mrs. C. C., Case No. 30, a white female, forty-three years of age, the diagnoses were as follows: (a) hypertension; (b) enlargement of the heart; (c) normal sinus rhythm, and heart failure of the congestive type. Hypertension was known to have been present for at least nine years, dyspnea, orthopnea, and ankle edema had been observed for three years, and during this period digitalis had been taken regularly. The signs of heart failure were as follows: many moist

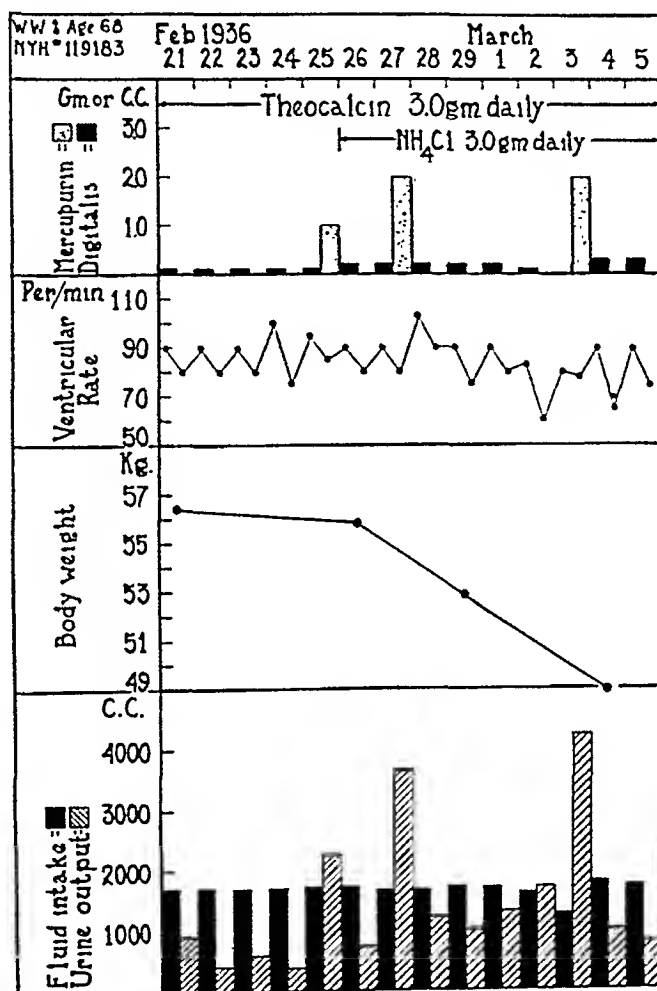


Fig. 4.—In this figure is represented the diuretic effect of mercupurin in W. W., Case No. 21, suffering from arteriosclerotic heart disease.

râles at the bases of both lungs, marked enlargement of the liver, and massive pitting edema of the lower legs, thighs, and sacral region. The administration of digitalis was continued. Because the output of urine remained low mercupurin was given also. It induced diuresis amounting to as much as 3,700 c.e. a day, and as a consequence the peripheral edema disappeared and the other signs of heart failure decreased; a satisfactory loss of weight was observed (Fig. 5).

The case of Mrs. P. A., Case No. 40, a white female, forty-four years of age, illustrates the effect of this drug in a patient suffering from chronic constrictive pericarditis of unknown etiology. Auricular fibrillation was present. She complained of swelling of the ankles for five months and swelling of the abdomen for two months before admission to the hospital. Fluid in both pleural cavities, moist râles

over the upper part of both lungs, marked enlargement of the liver, a large amount of ascites, and massive edema of both lower legs and thighs were the signs of heart failure. The exhibition of rest in bed, of restriction of fluid and salt, and of digitalis as well as theocaine not only failed to reduce the accumulations of fluid

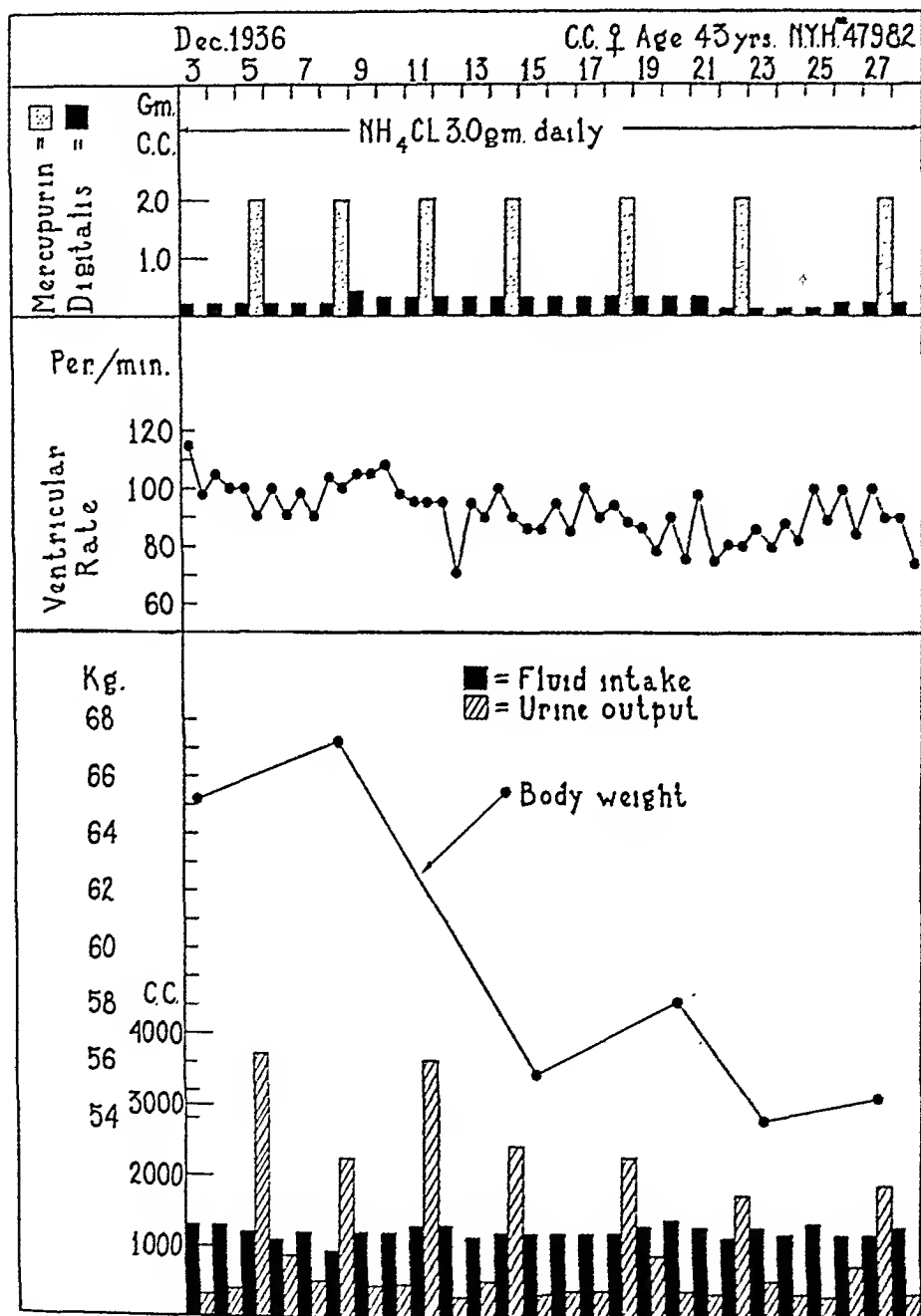


Fig. 5.—In this figure is shown the diuretic effect of mercupurin in C. C., Case No. 30, who suffered from hypertensive heart disease.

but were also ineffective in preventing further storage of it. When mercupurin was given at intervals of two or three days, excellent diuresis was obtained, the urinary output increasing to as much as 5,800 c.c. a day, the patient lost weight rapidly, and decrease in the clinical signs of heart failure was observed. The patient ap-

peared to gain weight in the intervals between the injections, so that it appeared that mercupurin alone was responsible for the failure of fluid to reaccumulate and weight to increase (Fig. 6).

The use of this drug in alcoholic cirrhosis of the liver when ascites is present is illustrated in the case of Mrs. C. K., Case No. 46, a white female, forty-four years of age (Fig. 7). On two previous admissions to the hospital the administration of salyrgan had proved ineffective in preventing the recurrence of ascites. When the patient came under our observation during her third admission she had been in the

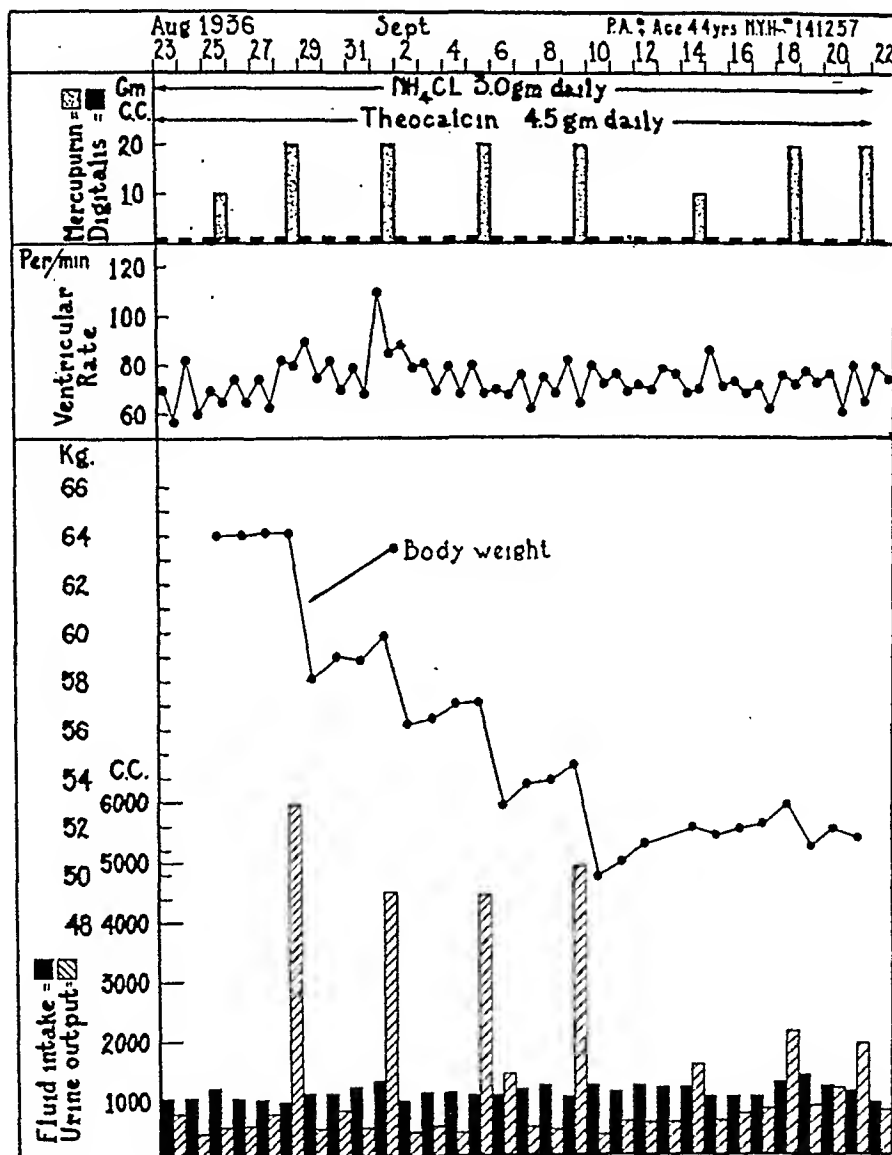


Fig. 6.—In this figure is represented the diuretic effect of mercupurin in the case of P. A., Case No. 40, suffering from chronic constrictive pericarditis. Ammonium chloride and theocalcin were given daily. Diuresis occurs on the days mercupurin was given.

hospital for twenty-one weeks. During this period it had been necessary to perform abdominal paracenteses at approximately ten-day intervals, and no decrease had been noted in the rapidity with which fluid recurred. A series of injections of mercupurin was then instituted and was found effective in preventing increase in the amount of ascites; the body weight remained relatively constant (Fig. 7). Mercupurin was then injected at weekly intervals for six months, both in the hospital and in the out-patient department. During this six months' period only four abdominal



paracenteses were required. The occasion for these arose in consequence of attempts to discontinue the use of mercupurin.

Certain observations are not brought out in the data presented in Figs. 1 and 2. For instance, 54 injections of merecupurin given to 31 patients gave diuresis which was definitely prolonged into the day following its administration. Its effect had disappeared on all occasions, however, by the end of forty-eight hours.

It was observed in general that the smallest diuretic effects occurred for the most part in patients in whom examination revealed little evi-

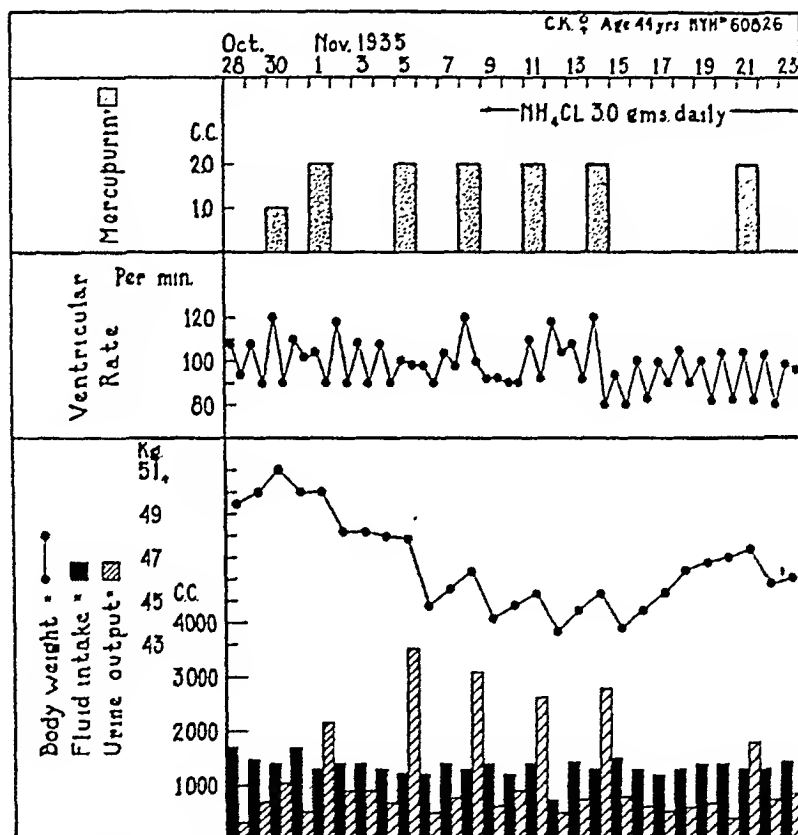


Fig. 7.—In this figure is recorded the diuretic effect of mercupurin in the case of C. K., Case No. 46, suffering from cirrhosis of the liver. The results of the first four injections may be compared with the last three in the period when ammonium chloride was being given.

dence of excess fluid, and that the largest effects occurred for the most part in patients in whom there were physical signs of massive accumulations of fluid. In short, it appeared that the amount of the diuresis was roughly directly proportional to the amount of excess fluid which was available for mobilization.

In 16 patients observations were made both with and without the simultaneous administration of ammonium chloride. It seemed possible in these to make an estimate of its influence on the diuretic effect of mercupurin. This analysis is, of course, open to the criticism that

the status of the patient when ammonium chloride was being given could not with certainty be said to be, and probably would not be, the same as when this drug was not given. Moreover, we have already directed attention to unexplained variation in the diuresis from time to time in the same patient. Nevertheless, in the case of 13 patients ammonium chloride appeared to augment the effect of mercupurin; on the other hand, in three other patients more marked diuresis occurred without the use of ammonium chloride. Most of the patients who gave consistently poor responses did not receive, for one reason or another, ammonium chloride. In the case of two patients who received urea daily for some time, the effect of mercupurin was greater while urea was being given than was the case before or after. In two other cases, however, the administration of urea failed to augment the diuretic effect of mercupurin.

Toxic effects were observed in only 3 of the 66 patients concerned in this analysis. On two occasions Mrs. P. A., Case No. 40, complained of nausea on the day of injection, and on two other occasions she experienced abdominal cramps, mild diarrhea, and slight acceleration of the pulse. It was observed that on each of these occasions there was diuresis of over 4,000 c.c. The physiological strain of excreting so large a volume of urine by a chronically ill patient may, however, account for these symptoms. The second patient possibly exhibiting toxic effects was Miss E. C., Case No. 39. This patient, a girl fourteen years of age, weighed, when free of excess fluid, only 29.0 kgs. She received 43 injections of mercupurin, usually 1.0 c.c. and occasionally 1.5 c.c., without untoward effects. On two occasions when 2.0 c.c. were given she experienced severe nausea on the day of injection. In view of her very small size the reaction occurred probably because the amount of mercupurin was too large. The third patient in whom the question of toxic effects arose was Mr. C. K., Case No. 55. Following two of the six injections which were given he experienced moderate diarrhea not associated with any other unpleasant symptoms. With these exceptions, however, no undesirable effect of mercupurin was observed in any of the 66 patients, many of whom received a large number of injections. Repeated examinations of the urine did not reveal evidence of renal irritation. The relatively low toxicity of mercupurin is well illustrated in the case of Mr. M. W., Case No. 11, who received three doses of 2.0 c.c. each without marked diuretic effect. He was then given 4.0 c.c. on three occasions. Two other patients, Mr. M. K., Case No. 8, and Mr. A. W., Case No. 47, also were given 3.0 c.c. on two occasions. On the occasions mentioned these larger amounts induced more marked diuresis without giving rise to undesirable toxic effects.

The drug was given to two patients in the nephrotic stage of chronic glomerular nephritis. In them there was observed no evidence of toxic effect on the kidney. Mrs. K. O. (Case No. 55, Figs. 1 and 2), a thirty-

eight-year-old woman, who had exhibited massive edema for one year, received 9 injections in a period of sixty-one days. Excellent diuresis resulted, associated with loss of 19.6 kg. in body weight. Mr. C. K. (Case No. 55, Figs. 1 and 2), a fifty-four-year-old man, who had suffered from massive edema for three years, and who was known to have had marked albuminuria during this time, received 6 injections in a period of thirty-two days. The urea clearance was 75 per cent of normal. Only moderate diuresis occurred. It was not effective in reducing the body weight because fluid reaccumulated during the intervals between injection. Examination of the urine of these two patients every two to three days did not show evidence of renal irritation and subsequent observation did not reveal evidence of decrease in renal function.

Venous thromboses and sloughs at the site of injection were not observed. In 5 patients the escape of appreciable amounts of mercupurin into the subcutaneous tissues occurred during injection. In each instance there was erythema, localized edema, and burning pain about the area. These persisted for one to two hours and disappeared. Further reaction did not ensue, however, in any case.

#### SUMMARY

Four hundred thirty-eight injections of the mercurial diuretic mercupurin were given to 66 patients who presented physical signs of excess fluid in the tissues. Fifty-two patients suffered from heart failure of the congestive type, nine from cirrhosis of the liver exhibiting ascites, two from the nephrotic stage of chronic glomerular nephritis, one from hydrothorax and ascites of unknown etiology, one from tuberculous of the peritoneum exhibiting ascites, and one from carcinomatosis of the pleura and peritoneum with hydrothorax and ascites. Each patient received from 1 to 45 injections; 2.0 c.c. was the dose usually given.

The results of 286 injections given to 57 patients appeared to represent the diuretic effect of mercupurin uninfluenced by other factors. A statistical analysis was made of these data (Figs. 1 and 2).

Mercupurin appears to be an excellent diuretic drug. It is our impression that it is at least equal and possibly superior to salyrgan in this respect. The diuretic effect varied between 200 c.c. and 5,900 c.c. but was most commonly between 1,000 c.c. and 2,000 c.c. Analyzed in another fashion, the urinary output was increased as much as nineteen times, but most frequently the increase did not exceed five times. These general statements may also be made: it appears to be equally effective irrespective of the etiological types of heart disease; the magnitude of the diuresis appeared to be roughly proportional to the amount of excess fluid stored within the tissues; ammonium chloride appears to enhance its diuretic effect; diuresis in patients suffering from cirrhosis of the liver exhibiting ascites appears to be less striking, al-

though the drug was frequently effective in preventing the recurrence of ascites; good results were obtained consistently in patients suffering from chronic constrictive pericarditis.

Effects which might have been construed as toxic occurred in only 3 patients, although the toxicity of mercupurin is open to question in two of these instances and was inconsequential in the third. On the other hand, mercupurin has the definite advantage that thrombosis or slough did not occur at the site of injection. It is our opinion that of the known mercurial diuretics, mercupurin is to be preferred when it is desired to mobilize fluid.

## REFERENCES

1. Bernheim, E.: Ueber das neue Quecksilberpräparat Salyrgan, als Diuretikum, *Therap. d. Gegenw.* 65: 538, 1924.
2. Von Issekutz, B., and von Végh, F.: Ueber die diuretische Wirkung organischer Quecksilberverbindungen, *Arch. f. exper. Path. u. Pharmacol.* 138: 245, 1928.
3. Herrmann, G., Schwab, E. H., Stone, C. T., and Marr, W. L.: On the Advantage of Alternating the Vegetable and Metallic Diuretics in the Treatment of Edema of Congestive Heart Failure, *J. Lab. & Clin. Med.* 18: 902, 1933.
4. DeGraff, A. C., and Batterman, R. C.: Reaction at Site of Injection of Mercurial Diuretics as Influenced by Theophylline, *Proc. Soc. Exper. Biol. & Med.* 32: 1,546, 1935.
5. Hahn, A.: Novurit, ein neues Diuretikum, *Wien. klin. Wchnschr.* 42: 1,477, 1929.
6. Popper, L.: Ein neues Quecksilber-Diuretikum "Novurit," *Med. Klin.* 25: 912, 1929.
7. Idem: Weitere Erfahrungen mit dem Quecksilber-Diuretikum "Novurit," *Med. Klin.* 25: 1,229, 1930.
8. Saxl, P.: Fortschritte der Diuresetherapie, *Wien. klin. Wchnschr.* 43: 916, 1930.
9. Spengler, G.: Zur Therapie der Leberzirrhose, *Wien. klin. Wchnschr.* 44: 257, 1931.
10. Engel, K., and Epstein, T.: Die Quecksilberdiuresese, *Ergebn. d. inn. Med. u. Kinderh.* 40: 187, 1931.
11. Pratsicas, A.: Das Quecksilber-Diuretikum "Novurit" in der Klinik, *Wien. med. Wchnschr.* 83: 28, 1933.
12. Crawford, J. H., and McDaniel, W. S.: Some Observations on Mercurial Diuretics, *Ann. Int. Med.* 8: 1,266, 1935.
13. Fulton, M. N., and Bryan, A. H.: Some Observations on the Comparative Effectiveness of Mercurial Diuretics With and Without Theophylline (Mercupurin, Salyrgan, etc.), *J. Lab. & Clin. Med.* 20: 1,252, 1935.
14. Steuer, L. G., and Wolpaw, S. E.: Diuretic Action of Mercupurin, *J. Lab. and Clin. Med.* 21: 298, 1935.
15. DeGraff, A. C., Nadler, J. E., and Batterman, R. C.: A Study of the Diuretic Effect of Mercupurin in Man, *Am. J. M. Sc.* 191: 526, 1936.

## EXTRACARDIAC DETERMINANTS OF THE SITE AND RADIATION OF PAIN IN ANGINA PECTORIS WITH SPECIAL REFERENCE TO SHOULDER PAIN\*

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A PAINFUL left shoulder is commonly encountered in patients with angina pectoris. Edeiken and Wolferth<sup>1</sup> have recently again called attention to this association. We refer not to the usual radiation of the substernal pain to the left shoulder and left arm, but rather to a continuous intractable pain in the shoulder, which is aggravated by movement of the shoulder, but not by walking, and which prevents sleep because the patient is unable to bear his weight on the joint. The shoulder is tender to touch, and there is, as a rule, sharp limitation of motion on abduction and external rotation. The clinical picture of these painful shoulders resembles that of so-called subdeltoid bursitis, or periarthrititis of the shoulder. Roentgen study rarely reveals calcification in the supraspinatus tendon. The condition is very persistent, and usually the pain is out of proportion to the demonstrable lesion in the shoulder.

The association of such painful shoulders with coronary artery disease and angina pectoris is too frequent to be accidental. The overwhelming preponderance of left-sided shoulder pain in patients with angina pectoris is significant. Of our 21 cases 16 were left-sided, and of Edeiken and Wolferth's 14 cases all but two were left-sided. Orthopedists, on the other hand, who see the general run of painful shoulders, report that the majority are right-sided.<sup>2</sup> Did such disability arise from traumatic causes alone, one would expect preponderant right-sided symptomatology, for most people are right-handed. Still more significant is the observation that patients with radiation of the anginal pain to the right shoulder and right arm may subsequently develop right-sided shoulder pain. Edeiken and Wolferth as well as Howard<sup>3</sup> report such cases.

Shoulder pain in patients with angina pectoris may give rise to varied clinical pictures. Most striking are patients who have been conscious of a mild disability and pain in the left shoulder, and who within a day or two following a thrombosis of a coronary artery develop severe, even agonizing, continuous pain in the left shoulder resembling that of a severe periarthrititis. The development of such shoulder pain within a week or two after an atypical attack of upper abdominal or chest pain, the diagnosis of which is in doubt, may give the first clue that a cardiac infarction was the cause of the attack.

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Read before The American Heart Association, section on cardiac disorders, June 8, 1937, at Atlantic City, N. J.

More often the association of left shoulder pain with the anginal syndrome is less dramatic. There are patients in whom the shoulder pain may antedate or may follow the coronary occlusion by many weeks or months, or even years. We have observed a man who had episodes of severe left shoulder pain at the ages of sixty-seven and sixty-nine years, who at the age of seventy-one suffered a coronary thrombosis, without having had preceding anginal symptoms; and who finally at the age of seventy-seven, one month after an attack of acute left ventricular failure, had a third severe attack of left shoulder pain. Not uncommonly there is an intensification of the shoulder disability whenever there is an aggravation of the cardiac condition.

Left shoulder pain is uncommon in forms of heart disease other than that due to coronary artery sclerosis, but we have seen it in a man with the anginal syndrome associated with calcific aortic stenosis, as well as in another patient following paroxysms of auricular fibrillation.

*Severe Shoulder Pain Following Coronary Thrombosis*

CASE 1.—A. G., a grocer, at the age of forty-seven years, had a sudden attack of constricting pain in the left chest which radiated to the left shoulder and lasted for a few minutes. Following this he had classical angina pectoris on effort. A year later, at the age of forty-eight he had severe attacks of anginal pain. Five days after an attack, which lasted twenty hours, he was admitted to Mount Sinai Hospital. The electrocardiogram on admission showed an abnormal R-T transition and a negative T-wave in Lead I which in five days changed into a typical coronary T-wave. Four days after admission he complained of precordial pressure, with radiation of pain to the left arm on the slightest movement in bed. Several days later he experienced a particularly severe attack of pain referred to the left arm and to the left side of the trunk and with this was unable to move the left shoulder and the fourth and fifth fingers of the left hand. The electrocardiogram revealed no further change. From this time on there were progressive pain and limitation of motion of the left shoulder. The pain was so severe that it required hypodermic medication with morphine. The arm could not be raised passively. Abduction and external rotation caused severe pain. The condition very slowly receded. At the time of discharge, three and one-half months later, there still was incomplete mobility of the left shoulder and distinct atrophy of the left forearm. He was re-admitted two months later. Movements of the shoulder caused pain and a creaking could be felt in the joint. There was atrophy of the muscles of the left arm and the forearm. There was hyperalgesia of the left forearm and of the chest. Five months later the shoulder pain persisted and the electrocardiogram at this time showed low voltage and slurring of the QRS in Lead I. The T-wave in Lead I was upright and was partially inverted in Lead III. (He was receiving digitalis at this time.)

*Illustrating Right-Sided Shoulder Pain With Right-Sided Radiation of Angina*

CASE 2.—P. F., a man fifty years of age, had had attacks of acute febrile polyarthritis at the ages of twenty-four and forty-one. He had no knowledge of an accompanying heart lesion. Beginning about Aug. 15, 1936, walking induced pain to the right of the sternum, which radiated to the right shoulder and which was associated with some difficulty in breathing. The symptoms compelled him to halt and were relieved by nitroglycerine. Excitement induced similar pain. On about Nov. 1, 1936, he developed continuous pain with limitation of motion in the right shoulder. This

pain was not induced or intensified by exertion and lasted about a week. Examination on Dec. 17, 1936, revealed a pasty complexioned man. The lungs were clear. Movements of both shoulders were free and painless. Fluoroscopy revealed slight enlargement of the left ventricle and of the left auricle. The first heart sound was dull. There was a systolic murmur at the apex, transmitted a short distance to the axilla. Blood pressure was 110 systolic and 80 diastolic. The electrocardiogram showed slurring of the QRS in all leads, Q-waves in Leads II and III, and a negative T-wave in Lead III. The QRS interval measured 0.12 second. The patient had an old inactive rheumatic mitral insufficiency, as well as an old infarction of the posterior aspect of the left ventricle.

This case illustrates not alone right shoulder pain with right-sided anginal radiation, but suggests that the onset of the shoulder pain marked the occurrence of a coronary thrombosis.

#### *Intensification of Shoulder Pain by Intercurrent Coronary Thrombosis*

CASE 3.—M. S., a man aged forty-nine years, had known of glycosuria since early in 1934. Beginning in March, 1933, and persisting for two years he had had pain in the right upper interscapular region, which radiated to the right lower anterior chest. This pain occurred only while he was resting in bed, was relieved by moving about and was not induced by exertion. In December, 1934, he complained of increasing tiredness and of some pain in the posterior aspect of the left shoulder which was intensified by movement of that joint. On March 15, 1935, he suffered an attack of right lower anterior chest pain which radiated to the angle of the right scapula and which lasted two days. With this there was intermittent cramping epigastric pain. Examination on March 18, 1935, revealed a man looking rather old for his years. The lungs were clear. Fluoroscopy revealed a heart of normal size and configuration. The aorta was elongated and dense. The heart sounds were of good quality. There were no murmurs. Blood pressure was 125 systolic and 85 diastolic. The electrocardiogram was normal in the conventional leads, but there was a very deep T-wave in Lead IV. He stayed in bed for two months. During this time he complained of a rather constant pain over the lower right ribs, both anteriorly and posteriorly. The pain was aggravated by movement of the trunk, but not by walking. Examination on May 13, 1935, revealed free movements of the spine and no bands of hyperesthesia. There was tenderness over the lower anterior ribs on the right side. The electrocardiogram now showed a small diphasic T-wave in Lead IV. In August, 1935, the right shoulder was very painful for a week. This cleared up and pain developed in the left shoulder which persisted for four months. In December, 1936, he had an attack of precordial pain in the region of the apex, which lasted one hour, compelling him to rest in bed for two weeks. There was no radiation of pain during the attack, but following the attack the left shoulder pain, which by this time had become minimal, became intensified and limitation of motion of the shoulder joint appeared. The electrocardiogram on Jan. 15, 1937, again revealed a deep T-wave in Lead IV.

This case illustrates intensification of shoulder pain by intercurrent attacks of coronary thrombosis as well as a shift from the right shoulder to the left shoulder as the anginal pain moved from the right of the sternum to the region of the apex.

#### *Relief of Anginal Pain by Pressure on the Brachial Plexus*

CASE 4.—S. R., a man aged fifty-seven years, had had typical angina pectoris since 1929. On Oct. 6, 1935, he had a nocturnal attack of severe cramping pain in both arms above the elbows, which lasted for ten minutes. There was no associated chest pain. Following this he developed distressing pain in the left shoulder which persisted for two months. There was no further angina on effort, but the shoulder was constantly troublesome and he was unable to use the left arm. Examination revealed moderate limitation of abduction and external rotation of the left shoulder.

Movements were limited by muscle spasm and severe pain. Libman's maneuver for the relief of this shoulder pain was attempted. A point was found over the left brachial plexus, pressure on which caused severe pain which radiated to the left shoulder and down the left arm. Strong pressure was exerted on this spot for about two minutes until the whole left arm became numb. This pressure caused agonizing pain, so that the patient perspired freely. Immediately after the cessation of the pressure, the pain in the shoulder disappeared and all movements of the arm and the shoulder were absolutely free. Complete relief lasted for twenty-four hours. Pain recurred then in milder degree and was relieved by ten diathermy treatments.

CASE 5.—I. R., at the age of forty-four years, in 1932, suffered a coronary thrombosis after having had angina pectoris on effort for two months. During the cardiac infarction there was sticking pain in both forearms. Following this he had anginal pain on effort without radiation to the shoulders or arms. When last seen in May, 1937, he stated that for two months he had felt pain in the right wrist on walking five blocks, as well as on change of weather. Six weeks after the onset of these symptoms he was awakened at night with severe pain in the right shoulder. He was unable to lie on his back. This pain persisted to the day of his examination ten days later. Abduction of the arm was limited to 90 degrees and there was pain on external rotation. Pressure on the right brachial plexus caused severe pain without radiation to the shoulder or arm. Strong pressure was thus exerted for one minute. Following this the shoulder pain was gone and movements of the shoulder joint were free. In putting on his coat the patient was surprised at the freedom from pain. A few moments before his wife had had to help him take off his coat because of the crippling pain in the shoulder. The cardiac status and electrocardiogram on the occasion of this examination were unchanged.

This case again illustrates right shoulder pain with right-sided anginal radiation, as well as successful relief by the Libman maneuver.

*Painful Left Shoulder in a Patient With Angina Pectoris Due to Calcific Aortic Stenosis*

CASE 6.—W. F., a man aged fifty-nine years, had had articular rheumatism as a child, and had known of a heart lesion since the age of twenty years. He was first observed at the age of fifty when he complained of dyspnea on climbing stairs and of transient attacks of faintness. Examination revealed a classical aortic stenosis and insufficiency with little cardiac enlargement. At the age of fifty-six he began to have a burning pressure under the sternum when walking after meals, sufficiently severe to compel him to stand still. This gradually became worse so that after three more years he could hardly walk one block. At the age of fifty-nine his left shoulder became painful. The pain was continuous and was intensified by abduction of the left arm. Examination two months after the onset of the shoulder pain revealed great enlargement of the left ventricle, moderate enlargement of the right ventricle and slight left auricular enlargement. There was a systolic thrill and murmur at the aortic area, as well as a diastolic murmur which latter was transmitted to the apex. Blood pressure was 120 systolic, 85 diastolic. The electrocardiogram which had been normal nine years previously showed inversion of  $T_1$ , diphasic  $T_2$  and  $T_3$ , and a very small initial downward deflection in Lead IV. The left shoulder, particularly its outer aspect, was tender and there was marked limitation of motion on abduction and external rotation. Nine days after this examination the patient died suddenly, six hours after an attack of severe precordial pain.

*Painful Left Shoulder in a Patient With Paroxysmal Auricular Fibrillation and No Demonstrable Organic Heart Lesion*

CASE 7.—P. F., a man aged forty-two, on Dec. 1, 1936, had a sudden attack of palpitation and dyspnea which lasted about an hour. He noted a rapid irregular beating of his heart. On April 8, 1937, he had a second attack which lasted two



and one-half hours. An electrocardiogram revealed auricular fibrillation with rapid ventricular rate and many extrasystoles. A third attack lasting two hours occurred on April 18, 1937. Ever since the first attack the left shoulder has been slightly painful, although movements of the shoulder were free. He observed that the shoulder pain on each occasion was intensified for about an hour after an attack of rapid palpitation. Examination on April 23, 1937, at a time when there was normal sinus rhythm was completely negative. No organic heart lesion could be demonstrated, the blood pressure was 120 systolic and 80 diastolic. The electrocardiogram was normal. There was no evidence of hyperthyroidism. The left shoulder was not tender and all movements were free and painless.

#### DISCUSSION

It is most important to distinguish this shoulder pain from the pain of anginal radiation. The patient can clearly differentiate the two. The shoulder pain is continuous, often intensified at night when the patient lies on the shoulder, aggravated by movements of the arm, but not by general body exercise, and there is limitation of abduction and external rotation of the arm. When angina and shoulder pain coexist, and when the shoulder pain is intensified by the angina on effort, nitroglycerine relieves the chest pain but not the shoulder pain. Many patients are kept in bed for weeks by their physicians in the erroneous belief that the persistent shoulder pain signals a progressive cardiac lesion. Although these painful shoulders are often initiated by an acute cardiac episode, they may persist for months without further progress of the heart lesion, and often yield to appropriate physiotherapeutic measures, in particular diathermy. At times they are miraculously cured by the maneuver described by Libman<sup>4</sup>—strong, prolonged pressure for one or two minutes on a sensitive point over the corresponding brachial plexus.

The mechanism of shoulder pain in patients with coronary artery disease remains obscure. The syndrome has been described by a number of observers. R. Schmidt<sup>5</sup> pointed out that in many patients with angina pectoris there are permanent sensitive spots, particularly the left brachial plexus. There is often tenderness along the spinal nerve roots from C7 to D4. Trophic disturbances such as herpes zoster, and hyperhydrosis have been observed in this distribution. There are arthralgias of the left shoulder and rheumatic myalgias in the area of trophic disturbance, as well as paresthesias of the left upper extremity which often persist between attacks. To explain all of these phenomena Schmidt assumed a neuralgic or neuritic condition of the cardio-aortic plexus, and postulated that the anginal attack just added a peak to a permanent state of excitation.

Libman has been interested in this phenomenon for years and in 1927<sup>6</sup> described a patient with angina pectoris and severe left shoulder pain, which radiated down to the fingers. The patient also had a cervical rib, and had had tingling and weakness of the hand, but no pain for

years. Libman concluded that the angina pectoris or a neuralgic condition of the cardiac plexus had sensitized the cervical nerves and had converted the tingling and weakness into severe pain. In 1935<sup>7</sup> he pointed out that a subacromial bursitis will begin to give pain shortly after a coronary thrombosis has occurred. He suggested that the frequent coexistence of shoulder pain and angina pectoris was determined by the fact that they were both caused by the same metabolic disturbance.

Lian<sup>8</sup> in discussing angina pectoris complicating left thoracobrachial neuralgias expresses the belief that the cervical neuralgia is the result of repeated "nerve shocks" caused by the frequent anginal seizures. The brachial neuralgia, in turn, may cause an ankylosis of the left shoulder. Lian believes that the reverse process can take place; that pure brachial neuralgias can give typical anginal radiations, and that in such cases a retrograde radiation takes place.

Edeiken and Wolferth suggest an analogy between shoulder pain and causalgia and that the sympathetic nerves may be concerned in the production of the pain. Interesting in this connection is a report by Kwan<sup>9</sup> of a patient with severe causalgia of the left arm following a bullet wound that had shattered the clavicle. At operation the brachial plexus was found imbedded in scar tissue and the axillary artery was obliterated. Dissection of the scar tissue and excision of several inches of axillary artery brought no relief. The pain ceased promptly following cervicothoracic ganglionectomy.

There is no satisfactory explanation of the manifestations of shoulder pain in patients with angina pectoris. A large group of associated and apparently related phenomena must be considered together in an attempt to gain an understanding of the mechanism involved. Shoulder pain occurs with exceptional frequency in patients with angina pectoris. With left-sided anginal radiation it is almost always the left shoulder that is involved. When the right shoulder is affected there is almost always right-sided anginal radiation. Other disturbances in the arm are often encountered, even in the absence of shoulder pain. One of the most striking is weakness or lameness of the left arm. This is a very common complaint of patients with left-sided anginal radiation. Recently we saw a man who had lost his anginal pain after having suffered a coronary thrombosis with right-sided radiation, but who was unable to work because of weakness of the right arm. Not uncommonly one sees inverse radiation in angina pectoris, the pain beginning in the fingers and traveling up the arm to the precordium. At times in such cases this inverse anginal seizure is provoked by use of the arm or by touching a cold object. Frequently, too, a patient will be able to walk quite freely without pain, but if he carries a light overcoat or brief case in the left arm he is stopped by an anginal attack after walking a short distance. Yet he can carry heavier articles in the right hand without distress.

At times lameness of the left arm when carrying light objects may be the first and only symptom of angina pectoris, the classical picture appearing months or years later.

Herpes zoster in skin areas corresponding to the distribution of the pain has been repeatedly described in patients with angina pectoris.<sup>10</sup> Cases of localized sweating in the shoulder and arm in anginal patients have been recorded.<sup>11, 12</sup> Hatiegan and Liviu<sup>13</sup> observed five patients who during their anginal attacks had painful contractures of the left upper extremity, especially of the fingers of the left hand. Bard<sup>14</sup> studied a man, aged thirty-three, whose left middle finger "went dead" during anginal seizures. Between anginal attacks the third toe of the left foot repeatedly became pale and cold. The patient died suddenly in an anginal seizure.

A more striking illustration of the relationship between the brachial plexus and referred precordial pain is found in the following case of Aronowitch.<sup>15</sup> A man, aged twenty-nine, had a neuroma giving rise to a severe neuralgia in the stump of his left arm that had been amputated at the lower third. At operation two neuromas were extirpated. Four days later severe pain in the left arm appeared. This was soon followed by air hunger and a feeling as though the heart had stopped beating. In addition there were crises of pain in the precordium, neck, and left shoulder as well as precordial oppression. Examination of the heart revealed no abnormalities. After drainage of a hematoma that had formed in the stump, the pain and the anginal seizures slowly disappeared.

Much has been written about pain in the left chest and shoulder girdle caused by arthritis of the cervical spine. Hanflig<sup>16</sup> observed that although the shoulder joint was painful its movements were not limited and there was no spasticity of the shoulder muscles. In patients with narrowing of the lower cervical intervertebral discs pain in the shoulders, arms, and precordium may occur, and with this there is often inability to raise the arm as in brushing the hair. But even in such patients passive movements of the shoulder are free.<sup>17</sup> Shoulder pain associated with angina pectoris is characterized by marked limitation of motion of the shoulder and spasticity of the muscles around the shoulder joint. This suggests that different mechanisms are involved in the two conditions.

Our first thought was that there was an independent affection of the shoulder, and that the radiation of anginal pain down the same sensitized pathway merely intensified the pain due to the local lesion. Carnett<sup>18</sup> believes that shoulder reference of pain and tenderness in biliary colic as well as in angina pectoris occurs only as an aggravation of a neuralgia, due to some extraneous cause. It is interesting that shoulder pain of the type seen in angina pectoris is not observed in patients with chronic gall bladder disease, although referred pain to the right shoulder is

very common. The distribution of anginal pain in patients with spondylitis, or with peptic ulcer or gall bladder disease, as will be described below, also suggests that sensitization of a dermatome by another disease process may determine the spread of anginal pain and increase its intensity. However, the weight of evidence points to a primary sensitization of the brachial plexus by afferent pain impulses from the heart.

Our own observations together with those culled from the literature reveal the frequent occurrence of sensory and trophic disturbances in the arm and shoulder which have been the seat of radiation of pain in anginal seizures. These neurogenic disturbances of the upper extremity differ in character and mechanism from the usual type of referred pain. The disorder persists long after the anginal attack, although it is usually intensified by recurrent attacks; there is no hyperesthesia of the skin in the corresponding dermatomes; the brachial plexus and some of the nerves derived from it are tender on pressure. The shoulder joint, which is so often the seat of a very painful affection, is innervated by the fifth and sixth cervical nerves, whereas cardiac afferent impulses enter the dorsal ganglia in the first five dorsal segments, but not at higher levels. Firm pressure on the homolateral brachial plexus evokes intense pain referred to the shoulder, and prolonged pressure may bring about instantaneous relief of the pain and limitation of motion of the affected shoulder (Libman).

Recent work on the electrophysiology of nerves has shown that periodic painful impulses are capable of building up intense activity in the central neurone and may thus give rise to constant pain. One would have to suppose that periodic cardiac afferent impulses are in this manner conducted to higher levels in the spinal cord, and that there a summation of their effects gives rise to continuous pain in the brachial distribution. The suggestion of Schmidt and Lian that a neuralgia of the cardio-aortic plexus gives rise to a brachial neuralgia explains nothing and is but a phrase. If some such mechanism obtains, then alcohol block of the first five thoracic ganglia on the affected side should, by eliminating the cardiac afferent impulses, lead to rapid subsidence of the shoulder and arm affection. We have not yet had opportunity to test this in a patient. According to this concept, too, shoulder pain occurring before manifestations of angina pectoris might in certain cases be evidence of cardiac afferent impulses of insufficient intensity to produce the anginal syndrome. This is in accord with Schmidt's observation that tenderness of the brachial plexus on the left side may antedate the appearance of the symptoms of angina pectoris.

The location and radiation of pain in patients with angina pectoris presents other puzzling phenomena. Years ago Mackenzie<sup>19</sup> drew attention to the fact that if a patient with angina pectoris had an abscessed tooth the anginal pain would radiate to that tooth.

The usual radiation of the pain of angina pectoris is along the course of C8 and D1 and D2, involving the precordium, left shoulder, and upper extremity. According to the theory of referred pain, if the sensory stimuli from the heart make irritable spinal segments other than those at their level of entry into the spinal cord, corresponding dermatomes are affected, the pain spreads (or radiates) and may be felt in the neck, face, scalp, abdomen, and even in the thigh. If a second disease process, e.g., an abscessed tooth, sensitizes a spinal segment at a level distant from the one corresponding to the heart, this distant area may be the sole seat of pain induced by and reflected from the heart. If the distant spinal segment is less highly sensitized, pain may be felt first in the dermatome corresponding to the heart, and secondarily in the distant area. Thus there may be radiation of pain to distant areas, with intervening silent zones.

The following cases illustrate these phenomena:

P. K., a woman aged forty-nine years, had known of glycosuria and hypertension for seven years. For twelve years weather changes had produced moderate tearing pains of all of her extremities. Since the age of forty-one, hurrying or going up stairs induced pain in the suboccipital area, which radiated to the scalp and to the thoracic and lumbar spine. The pain was severe and cutting in nature and associated with some difficulty in breathing. It compelled her to rest. The pain was relieved by strong pressure of the hand exerted over the back of the neck. In January, 1937, at the age of forty-nine, she had severe pain throughout the body as though it were "broken" and the right arm and neck were very painful. Some hours later the pain became more severe and radiated from the neck down the right arm. There was no chest pain. The blood pressure dropped from its usual level of 230 to 150 systolic, and the temperature rose to 102.5° F. and remained elevated for several days. Examination a few days later revealed as a striking finding marked tenderness of the right shoulder and inability of abduction and external rotation because of severe pain. The heart was enlarged to the left. The heart sounds were of good quality. Blood pressure was 200/90. She was reexamined five weeks after her attack. Fluoroscopy revealed moderate enlargement of the left ventricle. Blood pressure was 175 systolic and 75 diastolic. The electrocardiogram revealed a large Q-wave in Lead I. The T-waves were low and the R-T segment depressed in all leads. The shoulder pain and tenderness had disappeared and motion of the arms was free. There was no abnormality of the spine.

We believe that in this case there had been a mild spondylitis for twelve years which determined the radiation of the pain. The case, too, illustrates right-sided radiation with right-sided shoulder pain.

S. H., a woman aged fifty-nine years, had known of hypertension for one year. Ever since the age of thirty years she had had attacks of "lumbago," characterized by severe pain in the lumbosacral area, which would last for several days and confine her to bed. She had had her last attack at the age of fifty-four. In her fifty-eighth year she began to complain of lumbosacral pain which would radiate up the dorsal spine and would be associated with a sense of choking. This pain would come when she walked a few blocks quickly and would compel her to rest. She said that the pain would be unbearable if it lasted more than a few moments. Similar lumbosacral pain was induced by excitement. She was examined in 1937 at the age of fifty-nine. She was rather stout, with a pendulous abdomen. There were scattered

wheezes throughout both lungs. Fluoroscopy revealed slight enlargement of the left ventricle. The first heart sound was feeble. There were no murmurs. Blood pressure was 200 systolic and 100 diastolic. The electrocardiogram revealed very low T-waves in all leads, particularly in Lead I. The urine showed much sugar. There was no evidence of local disease or tenderness in the lower spine or in the sacroiliac region. She was given a reduction diet, as well as a corset to support her abdomen. She lost nineteen pounds in two months. She was able to walk much more freely and her attacks occurred less frequently. However, at the end of this period her niece died and on this occasion the patient had an attack of severe pain in the sacrum, radiating to the spine associated with a sense of choking which lasted only a few minutes.

In this case the anginal pain radiated to the sensitized lumbosacral spine.

Harlow Brooks<sup>20</sup> described a man who had had chronic appendicitis for years and who then developed angina pectoris. Effort regularly provoked pain in the right lower quadrant of the abdomen, which radiated to the sternum and down the left arm. A man with renal calculus regularly felt on exertion pain in the region of the affected kidney, associated with substernal oppression.<sup>21</sup> In another man with long-standing occipital neuralgia the anginal pain radiated to the back of the head.<sup>22</sup>

Well known are cases in which the pain of coronary thrombosis is referred to the epigastrium and is associated with vomiting, giving rise to the clinical picture of perforated peptic ulcer or acute cholecystitis. Ulcers of the stomach, or peptic ulcer of the esophagus may cause substernal pain that may radiate to the region of the cardiac apex and to the left shoulder. Such pain bears a definite relationship to the ingestion of food. The usual site of pain in peptic ulcer is in the epigastrium. It may radiate to the entire abdomen and to the lower anterior chest.

When a patient with a peptic ulcer develops coronary artery disease, the ulcer pain may follow the distribution of the anginal pain. This is exemplified by the case of a man, aged fifty, who had nocturnal epigastric pain that radiated to both axillae and down the inner aspects of both arms to the elbows. The pain was relieved by a warm drink. Identical pain occurred an hour after meals. The same pain, however, was induced by walking a few blocks and compelled him to stop. Following treatment in the hospital, the spontaneous pains after meals disappeared, but walking a few blocks produced substernal pressure and pain in the right shoulder compelling him to halt. Five weeks after the onset of his symptoms he had a hematemesis and blood in his stools. X-ray studies showed the presence of a duodenal ulcer. The electrocardiogram showed left axis deviation, a sharply negative T-wave in Lead I and an abnormal R-T segment in Lead II. This patient had both angina pectoris and a duodenal ulcer, and the ulcer pain radiated down the sensitized cardiac pathways. Treatment induced a remission of the ulcer pain, but the angina on effort persisted.

L. D., a male, at the age of thirty-eight had had, for a period of four weeks, lower sternal pressure shortly after meals and lasting half an hour, associated with heaviness of both arms and difficulty in raising the shoulders. Such pain occurred frequently at night and lasted one to two hours. Roentgen studies of the stomach at that time were said to be negative. The symptoms remitted spontaneously and he remained in good health until the age of forty-nine, when on Nov. 16, 1936, one hour after lunch, he experienced sudden lower sternal pressure with pain radiating up both sides of the face, lasting about an hour. There was no sweating. He continued at work and two days later there was a recurrence of similar pain radiating to the face, which lasted all night. During the following two and a half weeks this pain with facial radiation appeared regularly half an hour after meals. He entered Mount Sinai Hospital on Dec. 6, 1936, at which time the pain was not definitely related to meals and lasted for hours on end. It was situated over the lower sternum and radiated to the face. The patient was given a strict Sippy diet and milk drip therapy and the pain ceased. An electrocardiogram taken at this time revealed evidence of a recent cardiac infarction. Roentgen study of the gastrointestinal tract showed a gastric ulcer. Following his discharge from the hospital he noted fatigue after walking half a block, compelling him to slow his pace. He never felt actual chest pain or pressure on exertion. When last examined in February, 1937, he had no abdominal tenderness. Fluoroscopy revealed some enlargement of the left ventricle and left auricle. The first heart sound was loud; there was a systolic murmur at the apex. The blood pressure was 115 systolic and 70 diastolic. The electrocardiogram showed a negative T-wave in Lead I, an absent initial downward deflection and an upright T-wave in Lead IV.

This man had had a gastric ulcer eleven years previously. In November, 1936, he had a coronary thrombosis marked by pressure over the lower sternum and radiation of pain to the face. Shortly thereafter he developed typical periodic ulcer pain, with the same radiation as the cardiac pain, which was relieved by a Sippy regimen. The ulcer pain followed the pattern previously laid down by the anginal radiation.

At times ulcer pains may have a typical anginal radiation in the absence of objective evidence of coronary artery disease and of angina on effort. In such cases one should suspect the presence of a latent coronary sclerosis. Illustrative of this is a man, aged fifty-four, who six years previous for two weeks had dull pain in the left parasternal region occurring about 3 P.M. and lasting about one-half hour, and relieved by alkali and by milk. The pain was unrelated to exertion. Three years later there was a recurrence of similar symptoms for a brief period. He was then well until a month before his examination, when he began to notice left parasternal pain, which radiated to the epigastrium and to the left shoulder. The pain awakened him almost every night. It began in the epigastrium and radiated to the precordium and left shoulder and was relieved by bicarbonate of soda. Walking did not produce the pain. Physical examination, in particular of the heart and abdomen, was completely negative. The electrocardiogram was normal. Roentgen study revealed a duodenal ulcer. The symptoms were promptly relieved by a Sippy diet. When seen one and a half

years later, he was symptom free. Examination and electrocardiography of the heart again were normal.

Pain arising in a diseased gall bladder may simulate the pain of angina pectoris, and in such cases it is difficult to determine which of these organs is giving rise to the symptoms. It has been shown experimentally in human subjects that inflation of the common bile duct by means of a rubber balloon may cause pain referred to the precordium.<sup>23</sup> In the presence of a normal heart it is unusual for the pain of gall bladder disease to radiate to the precordium. In patients who have both gall bladder disease and coronary artery disease the pain provoked by the cholecystic disease may radiate to the precordium and left arm. Lian<sup>24</sup> has reported the case of a man with angina pectoris and gall bladder disease in whom pressure over a palpable gall bladder repeatedly provoked anginal crises with radiation down the left arm. We have recently seen a similar case.

B. R., a man aged fifty-six years, had had classical angina pectoris on effort for five years. He has been observed in the cardiac clinic at Mount Sinai Hospital since July, 1933. A study in December, 1934, revealed a heart of normal size and configuration. The electrocardiogram showed the QRS complex slurred in Leads I and IV, the T-wave negative in Lead I, diphasic in Lead IV, and an absent initial downward deflection in Lead IV. Roentgen study of the gall bladder with dye was normal. He entered the hospital in May, 1936, because of right upper quadrant pain. One and one-half months previously he had had an attack of such pain which had lasted two days, for which he had received a hypodermic injection. Twelve days before admission colicky right upper quadrant pain recurred and persisted to the day of his entry to the hospital. Examination at this time showed a temperature of 101° F., a white cell count of 18,900 with 76 per cent of polynuclear leukocytes. The patient was hypersensitive. The first heart sound was feeble. The pulmonic second sound was accentuated. The blood pressure was 150 systolic and 100 diastolic. There was marked tenderness in the right upper quadrant and the liver could be felt extending three finger-breadths below the costal margin. Pressure in the right upper quadrant, particularly in the anterior axillary line, caused pain beneath the examining finger, as well as pain to the left of the sternum and difficulty in breathing. There was no trapezius or brachial plexus tenderness on either side. In the course of ten days the temperature and blood count returned to normal. The blood pressure dropped to 115/75, and the tenderness in the right upper quadrant gradually abated. On about the eighth day pressure in the right upper quadrant caused no local pain, but did cause sharp pain referred to the precordium. The electrocardiogram revealed a small Q-wave and a flat T-wave in Lead T, and an absent initial downward deflection and a diphasic T-wave in Lead IV. The gall bladder was not visualized on x-ray film after the administration of dye.

In this case a man who had had coronary artery disease for some years developed an acute cholecystitis. Pressure over the gall bladder provoked sharp precordial pain.

The interpretation of such cases is not as simple as it seems. When there is unequivocal evidence of coronary artery disease it may be assumed that the pain from the gall bladder radiates down the sensitized



cardiac pathways. But studies of Fitz-Hugh and Wolferth<sup>25</sup> seem to indicate that at times the gall bladder disease may cause injury to the myocardium, giving rise to anginoid pains and T-wave changes in the electrocardiogram, and that after operative cure of the gall bladder condition the precordial pain may completely disappear and the electrocardiogram return to normal. We have seen a patient who seems to fall in this category.

H. G., a man, was first seen in 1932 at the age of forty-one years. In 1930, following a bowel movement he suffered severe cramping pain in the entire abdomen. With this he perspired freely, and had marked palpitation. He recovered quickly and a few weeks later had a similar attack. On both occasions he was able to work the day after the attack. In 1932 he complained that for two months he had been having sharp momentary stabbing pains in the precordium while walking, which compelled him to stop. When he was tired he felt a continuous pressing sensation in the precordium which was aggravated by walking, but this did not compel him to stop whatever he was doing. Examination at that time was negative. He was obese. The heart was not enlarged; the heart sounds were of good quality. The blood pressure was 118 systolic and 80 diastolic. The electrocardiogram was normal. He was seen again in February, 1937. He had had a herniotomy in June, 1936, and two months later had had an attack of lower abdominal cramps, with sharp precordial pain about the apex, and vomiting. He was in bed for one week after this attack. In December, 1936, he was awakened at night by severe sticking apical pain with difficulty in breathing. Deep inspiration reproduced the precordial pain. In February, 1937, he had a similar attack with fever followed by two milder attacks on the following days. The precordial pain was relieved by nitroglycerine. On the third day he became icteric. Physical examination was negative except for moderate jaundice. The heart showed no abnormalities. The electrocardiogram, however, revealed T-waves that were practically flat in the three conventional leads. He was admitted to Mount Sinai Hospital where a cholecystectomy and a common duct exploration were performed. Gravel was found in the common duct. The gall bladder showed a chronic cholecystitis. Recovery was uneventful. He was seen six weeks after the operation. He was completely free from all symptoms. The electrocardiogram was normal; the T-waves again were of normal configuration.

Has this patient both gall bladder disease and coronary artery disease, or were the cardiac pain and the myocardial damage as shown by the electrocardiogram secondary to the gall bladder affection?

#### SUMMARY

An affection of the shoulder characterized by pain, muscle spasm, and limitation of motion occurs commonly in patients with angina pectoris. With rare exceptions the left shoulder is involved when there is left-sided radiation of anginal pain; the right shoulder when there is right-sided radiation. This shoulder pain is continuous, is not exaggerated by factors that usually induce anginal pain, but is often aggravated by sudden progress of the heart lesion, such as coronary thrombosis or acute left ventricular failure.

Such shoulder pain does not call for bed rest and treatment of the heart, but is relieved by local physiotherapeutic measures. At times the

Libman maneuver—firm pressure on the homolateral brachial plexus—brings about instant relief of this pain and limitation of motion.

The mechanism of this shoulder pain remains obscure. Certain analogies suggest that the radiation of the anginal pain to the shoulder superimposed on a local slightly painful affection of the shoulder may by summation induce this painful disablement. However, the many other trophic and sensory disturbances that may occur in the left upper extremity in patients with angina pectoris, suggest rather that the chief factor lies in some reciprocal relationship between afferent impulses from the heart and sensitization of the neurones whose fibers go to make up the brachial plexus.

The site and radiation of anginal pain may be determined by extra-cardiac lesions, such as abscesses of the teeth or spondylitis. In such cases the anginal pain may be experienced only or chiefly in the area sensitized by somatic disease.

Conversely in the presence of peptic ulcer or of gall bladder disease the pain arising in the ulcer or in the gall bladder may follow the anginal radiation.

Fitz-Hugh and Wolferth's observation is confirmed that there are patients with gall bladder disease, with reference of the pain to the precordium and T-wave changes in the electrocardiogram, in whom operative removal of the gall bladder is followed by disappearance of precordial pain and a return to normal of the electrocardiogram.

#### REFERENCES

1. Edeiken, J., and Wolferth, C. C.: Persistent Pain in Shoulder Region Following Myocardial Infarction, *Am. J. M. Sc.* 191: 201, 1936.
2. Dickson, J. A., and Crosby, E. H.: Periarthritis of Shoulder. Analysis of Two Hundred Cases, *J. A. M. A.* 99: 2252, 1932.
3. Howard, T.: Cardiac Pain and Periarthritis of the Shoulder, *M. J. & Rec.* 131: 364, 1930.
4. Libman, E.: In discussion of "A Review of Eighteen Months' Experience With Total Ablation of the Thyroid for Angina Pectoris and Congestive Failure," by H. L. Blumgart and D. D. Berlin, *J. A. M. A.* 104: 17, 1935.
5. Schmidt, R.: Zur Kenntnis der Aortalgien (angina pectoris) und über das Symptom des anginösen linksseitigen Plexus-Druckschmerzes, *Med. Klin.* 18: 6, 1922. Kardialgen und Aortalgien, *Med. Klin.* 31: 105, 1935.
6. Libman, E.: Address, Proc. Staff Meet., Mayo Clin. 2: 273, 1927.
7. Libman, E.: Symposium; Angina Pectoris With Special Reference to Coronary Artery Disease, *Bull. New York Acad. Med.* 11: 427, 1935.
8. Lian, C.: De l'angine de poitrine compliquant les névralgies thoraco-brachiales gauches, *Rev. belge sc. méd.* 3: 354, 1931.
9. Kwan, S. T.: The Treatment of Causalgia by Thoracic Sympathetic Ganglionectomy, *Ann. Surg.* 101: 222, 1935.
10. Wertheimer, R.: Herpes zoster bei angina pectoris, *Wien. klin. Wchnschr.* 40: 623, 1927. *Wien. klin. Wchnschr.* 41: 26, 1928.
- Winternitz, M.: Verein deutscher Ärzte. June 15, 1928, abstracted in *Med. Klin.* 24: 1650, 1928.
- Parsonnet, A. E., and Hyman, A. S.: Herpes Zoster and Angina Pectoris, *Ann. Int. Med.* 3: 883, 1930.
11. Palmer, R. S.: Localized Sweating, a Sympathetic Reflex Phenomenon in Angina Pectoris, *AM. HEART J.* 5: 519, 1930.
12. Holt, E.: Localized Sweating Replacing Cardiac Pain, *AM. HEART J.* 5: 522, 1930.

13. Hatiegan, J., and Liviu, T.: A New Symptom of Angina Pectoris (Viscero-Motor Phenomena of the Hand), *Cluj. med.* 6: 37, 1925.
14. Bard, L.: Angine de Poitrine et asphyxie locale des extremities, *Presse méd.* 29: 73, 1921.
15. Aronowitsch, G. D.: Ueber anginoide Anfälle bei Schmerzen im linken Brachial plexus, *Klin. Wchnschr.* 4: 117, 1925.
16. Hanflig, S. S.: Pain in the Shoulder Girdle, Arm and Precordium Due to Cervical Arthritis, *J. A. M. A.* 106: 523, 1936.
17. Turner, E. L., and Oppenheim, A.: A Common Lesion of the Cervical Spine Responsible for Segmental Neuritis, *Ann. Int. Med.* 10: 427, 1936.
18. Carnett, J. B.: Pain and Tenderness of the Abdominal Wall, *J. A. M. A.* 102: 345, 1934.
19. Mackenzie, J.: A Case of Angina Pectoris Associated With Great Excitability of the Vaso-constrictor Mechanism, *Heart* 2: 265, 1911.
20. Brooks, H.: Angina Pectoris, New York, 1929, Harper & Brothers, p. 20.
21. Mainzer, F., and Josephthal, P.: Ueber die Lokalisation und Ausstrahlung des Angina pectoris Schmerzes, *Acta med. Scandinav.* 89: 329, 1936.
22. Danielopolu, D.: L'Angine de Poitrine et l'Angine Abdominale, Paris, 1927, Masson & Cie, p. 13.
23. Doubilet, H.: Personal communication.
24. Lian, C.: L'angine de Poitrine, Paris, 1932, Masson et Cie, p. 261.
25. Fitz-Hugh, T., and Wolferth, C. C.: Cardiac Improvement Following Gall-bladder Surgery, *Ann. Surg.* 101: 478, 1935.

## SIXTEEN YEARS' EXPERIENCE WITH HEART DISEASE IN PREGNANT WOMEN

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THIS is a brief review of sixteen years' experience as cardiologist at the Boston Lying-In Hospital. There were more than 44,000 deliveries, 850 of the patients being classed as cardiacs, during this period.

Angus MacDonald of Edinburgh published a description of 29 pregnant women with severe heart disease in 1878.<sup>1</sup> I will quote a part of his first description. The patient was thirty-four years old, and had mitral stenosis. She had no disability until the seventh month in her first pregnancy when she caught a cold and had congestive heart failure. This was cured by a regime and digitalis and she was delivered successfully at term.

. . . She felt much better after her confinement, and suckled her child; and her health remained good till she became pregnant for the second time. Towards the middle of this pregnancy she became very markedly anaemic; her breathlessness, palpitation, and general discomfort returned, and her legs became enormously oedematous. About the end of the seventh month there was present general oedema, with cough and orthopnoea. I intended about this time to arrange for a consultation, with the view of deciding upon the propriety or otherwise of inducing premature labour, as Mrs. S. was now unable either to lie down or move herself in bed, so much pulmonary oedema and general anasarca were present. But on the 18th of May, 1872, the patient, being near the end of the eighth month, fell in labour. The delivery was easy. I gave chloroform with some hesitation at first, but it was well borne, though the pulse was exceedingly weak and very irregular. Mrs. S. did not improve much after the completion of labour. The anasarca and the dyspnoeic symptoms continued, and she was scarcely able to take any food. Her condition remained much at a standstill, however, till the morning of the sixth day after her delivery, when she suddenly fell back in bed dead.

Before 1921 somewhat similar cases furnished almost 25 per cent of all the maternal deaths at the Boston Lying-In Hospital. At this time the only convincing modern information on the subject was Sir James MacKenzie's<sup>2</sup> statements (1) that patients with auricular fibrillation did not do well in pregnancy, (2) that when cardiacs died in pregnancy, death was due to congestive heart failure, and (3) that the earliest sign of heart failure was persistent râles at the lung bases.

In the first three years of my service, 72 patients with severely damaged hearts were delivered. Eight died. Twelve of these had severe congestive heart failure as described by MacDonald. Faced with such women in the last trimester of pregnancy, we felt that for any likeli-

<sup>1</sup>Read before The American Heart Association, section on cardiac disorders, at Atlantic City, N. J., June 8, 1937.

hood of lasting relief the uterus must be emptied. Accouchement forcé had already been shown to yield a high death rate in such cases. Eleven of the failing cardiacs were therefore delivered by abdominal hysterotomy. It was found that (1) the patient survived the operation, but 50 per cent died days later; (2) there was no apparent marked amelioration of symptoms directly following emptying the uterus. This method of treating heart failure in pregnancy was, therefore, abandoned, and persistent effort made to relieve the failure before attempting delivery. The results were better, but still 25 per cent of such patients died. For thirteen years emphasis has been placed where it belongs on early classification, selection, and stubborn control of the cardiac in pregnancy.

From the beginning we have used a very simple *classification* based on direct examination of the heart and it has proved to be sound. The patients in the heart clinic fall naturally into three groups:

I. Those who have unmistakable evidence of severe heart damage, either (1) enlargement, or (2) a diastolic murmur, or (3) signs or history of heart failure, or (4) a dangerous disorder of the heart beat.

II. Those who have less evidence of heart damage, for example, doubtful enlargement, a systolic murmur.

III. Those with cardiac neurosis, N.C.A., or other perhaps disabling symptoms, but no evidence of heart damage.

Recognizable heart failure has not been found except among those who could be placed in Group I. Twenty per cent of the Group I cardiacs showed some form of recognizable heart failure during pregnancy. So far as pregnancy is concerned, no woman need be considered a "cardiac" unless she has the criteria for Group I. Of 850 such cardiacs delivered, 781 were considered to have rheumatic heart disease. The remaining 69 fell into small groups that must be considered distinct problems—congenital heart, enlargement with hypertension, cardiovascular syphilis, thyroid heart, blocks and other disorders of the heart beat. The prognosis and the nature of the dangers to be feared differ greatly in these groups.

*How can we subdivide the 781 rheumatic heart disease cases in respect to their prognosis in pregnancy?* A natural subdivision of the Group I cardiacs appeared early in the study and has proved its value, namely, Group I cardiacs who have (1) already developed recognizable heart failure, or (2) a complication in itself dangerous. The only common complication has proved to be auricular fibrillation, and this is surprisingly rare. Only 18 cases have had it either established or as a transient event. The maternal death rate is thirty-three and one-third per cent. Sir James was right, though he did not suspect its rare occurrence. Only one out of seven of all the fatal cases among the cardiacs had auricular fibrillation at any time.

Cardiacs classified as Group Ia when first seen (on a basis of previous congestive heart failure) have had a maternal death rate of 16 per cent.

Cardiacs classified as Group I when first seen have a maternal death rate of 3.5 per cent. Cardiacs classified as Group I who have not developed heart failure and therefore changed their status to Ia during pregnancy have a maternal death rate of 2.3 per cent. Whatever other classification one may like to use, these natural groupings must be respected. These statistics give us something definite to tell our patients and to direct us in their care. They comprise all that is surely known about the prognosis of patients with rheumatic heart disease in pregnancy. It is reckless to try to state the risk for any single case with accuracy. One can only guess a somewhat greater or less risk for the individual within these classes. Minor differences in the degree of heart damage are not directly pertinent to the problem of prognosis in pregnancy. For one illustration: one would expect a higher death rate where aortic regurgitation is added to mitral stenosis than with either valve lesion alone. But the maternal death rate differed only three-tenths of one per cent in patients with mitral stenosis with aortic regurgitation or with both, from the average death rate of all three. Patients with uncomplicated mitral stenosis differ greatly, of course, in their pathological signs and in their ability to exert themselves. But until they have developed auricular fibrillation or have already shown congestive heart failure, there are no clear subdivisions that appear to affect the prognosis in pregnancy. Only 10 per cent of those diagnosed as mitral stenosis had early mitral stenosis according to Lewis' standards—namely, a mitral diastolic murmur heard only after exercise with the patient recumbent. Some of these have had severe congestive heart failure. It is interesting to note that in the group with enlargement of the heart and no valve lesion diagnosed (52 cases), the death rate is 1.9 per cent. Nevertheless, these patients we still believe have deserved Group I cardiac care. The 1.9 per cent death rate has been in spite of such care. Congestive heart failure can appear and has appeared in this group.

Leaving now the question of prognosis—*how do the cardiacs die?* Sixty per cent of the deaths, before the last four years, were in and from congestive heart failure alone. Twenty per cent more died in congestive heart failure with some other important factor—for example, embolism, sepsis, ruptured appendix. Recognizable heart failure in Group I cardiacs in pregnancy has appeared as follows: Five only had the symptom of angina. All five of these had rheumatic heart disease with aortic regurgitation. Five had paroxysmal dyspnea. These had either aortic regurgitation or severe hypertension. No case with uncomplicated mitral stenosis has had paroxysmal dyspnea. There have been no sudden unexpected deaths attributable to the heart. Embolism from intracardiac thrombi was diagnosed only twice (both recovered), except in cases with bacterial endocarditis. As Sir James noticed, heart failure in pregnancy appears as congestive heart failure. Though the incidence of heart failure has not greatly diminished with improved care

and markedly lowered maternal mortality, it has changed its degree. Congestive heart failure no longer means the patient described by MacDonald, but an almost subclinical condition discovered by the examining physician. The maternal mortality of all those who had congestive heart failure during pregnancy formerly was 25 per cent. It is now 8 per cent. Heart failure is not what it used to be. The first reliable sign is persistent râles at the lung bases. There are earlier signs of failure—diminished vital capacity, Hoover's sign, and perhaps, rarely, increased venous pressure, but they are not reliable. We have tried in many ways to establish some useful earlier criterion, but all we have been able to add to Sir James' statement is the word "reliable."

What makes hearts fail in pregnancy? It is instinctive for a physician faced with a cardiac patient early in pregnancy, or contemplating pregnancy, to direct his attention to the question, "Can this woman stand delivery and the strain of labor?" And indeed there is justification for

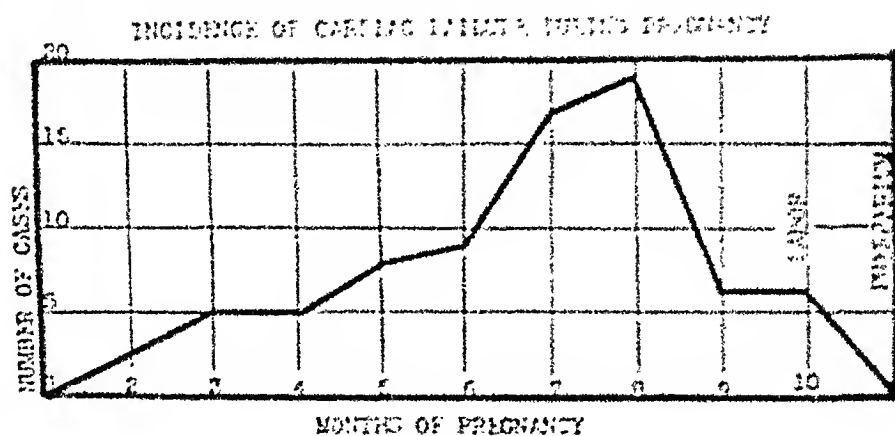


FIG. 1.

this in that 75 per cent of the deaths among the cardiacs occur in the short period of the puerperium. Only 25 per cent die during the months of pregnancy undelivered. The actual load of pregnancy on the circulation shows clearly during the first two-thirds of the last trimester, the blood viscosity and the hematocrit figures fall, and then rise sharply during the last few weeks before term, to continue the rise to normal after delivery with no abrupt change at the time of delivery. Similarly the total blood volume and the cardiac output rise and fall. Most important of all, the time at which recognizable heart failure has clinically appeared in pregnancy agrees with these indirect observations.<sup>2</sup> Failures cluster in the last part of the sixth and in the seventh and eighth months. They rarely begin in the last few weeks. In only four or five cases has failure appeared for the first time during or following the strain of labor and delivery. Delivery and its after effects appear in the study of these cardiacs who die in the puerperium as a good-sized last straw. Delivery will not put them into failure nor kill them unless they are already half dead.

This is a remarkable fact. This actual load of pregnancy should be visualized whenever we face a Group I cardiac early in pregnancy or who is contemplating pregnancy. Furthermore, in individuals the load of pregnancy shows itself, so far as we are able to find it, at varying times and in varying degrees of severity during the dangerous period. This great, varying and inevitable load of course makes it impossible to predict early in pregnancy how any heart will behave, except in a very general sense, by reasoning backward in the light of long experience with clearly defined groups. By no refinement of examination or effort test can we rightfully expect to determine that this or that patient will not develop failure. We can anticipate the coming load and make allowance for it in the regime of the patient. By routine weekly examination—long made a rule—we can watch for and detect failure early and treat it adequately.

Though the failures that occur in Group I cardiacs cluster at the time when the load of pregnancy on the circulation is heaviest, *determining causes for the onset of individual failures* stand out if we take case histories carefully. The same causes occur again and again: (1) Fatigue. One cannot put too much attention on the causes and effective prevention of this vague but vital factor. The commonest factors in fatigue are long shopping trips, moving, opening and closing summer homes, entertaining, sickness in the family. Sudden unusual exertion is a rarer cause. (2) Removable indirect loads on the heart. Overeating with gain in weight, excessive fluid intake, anemia, chronic infection such as oral sepsis, all can be shown to be common and real factors in the production of failure. These factors can be eliminated. The importance of this aspect of the problem cannot be exaggerated. It is unfortunate that it cannot be effectively described in brief.

*The Rôle of Intercurrent Infections in Producing Heart Failure and Death.*—Every patient has some kind of respiratory tract infection during the nine months of pregnancy or puerperium. If such patients continue to work, a certain number of them show signs of congestive failure. If they go to bed at the onset of the illness, nothing happens. Undoubtedly a severe epidemic such as occurred in 1918 and 1919 would play havoc with the cardiacs in pregnancy, but the epidemics, in the sixteen years that we have followed these cases, have been mild enough so that no death could be directly attributable to them until one death during the last year. Only one has developed pneumococcus pneumonia. This was in the puerperium. She recovered.

I have discussed these rheumatic heart disease cases as though their heart disease were stationary, and indeed it so appears. *In only seven instances have we been tempted to diagnose active rheumatic disease in a pregnant woman.* These were mild affairs. This statement challenges discussion, but it can be abundantly supported. Of course, cases can be found in which an individual, starting with rheumatic disease in



childhood, continues to have recurrences long into adult life and until death. Such cases may have had pregnancies. We find occasionally an individual followed through succeeding pregnancies, with at first nothing but a systolic murmur, years later a mitral diastolic, and later, an aortic diastolic murmur. Such cases are pleasingly scarce. Why do not these women develop active rheumatic disease during pregnancy? They are not the survivors of a group of rheumatic girls followed from the beginning of their disease. They are taken from the whole community—discovered among pregnant women who report to the hospital because they are pregnant and not because they have heart disease or rheumatic disease. Only 50 per cent have an adequate history of having had rheumatic disease. According to our present conviction, they must have had it, but perhaps in a comparatively mild form. In the 50 per cent

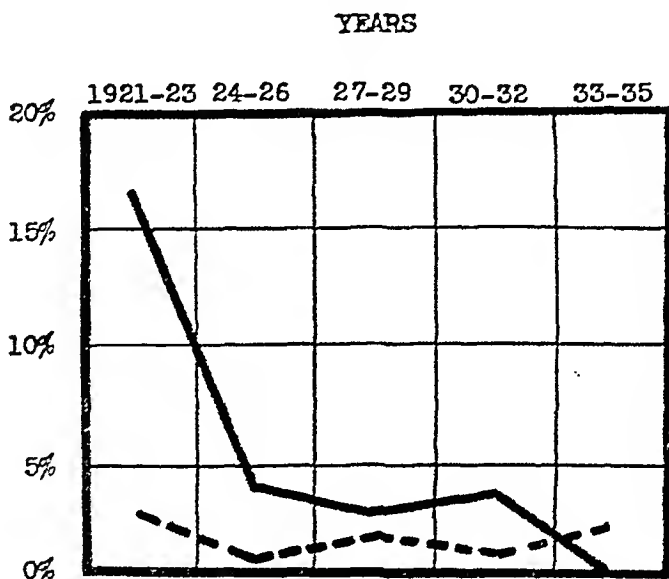


Fig. 2.—Upper curve represents maternal mortality in congestive heart failure per cent cardiae delivered. Lower curve (interrupted line) represents maternal mortality from causes other than heart failure per cent cardiae delivered.

that have an adequate history of rheumatic disease, the average age at clinical onset of the disease was thirteen and one-half years. The average age of the Group I cardiae in pregnancy is between twenty-seven and twenty-eight years. It has been a constant surprise to us to see evidence of activity fail to appear. The inference is that if one thinks of rheumatic disease as seen in medical clinics and, perhaps, at post-mortem study, one may have an exaggerated picture of its persistence and virulence in the adult with chronic rheumatic heart disease.

To return to the prognosis of a Group I cardiae patient in pregnancy. It would appear from all this that after eliminating the clearly bad risks such as described under Group Ia, it should be possible to prevent deaths in congestive failure among Group I cardiae by regimes designed to anticipate and allow for the load of pregnancy and to prevent the in-

cidental determining factors. And, in fact, deaths from congestive heart failure in pregnancy have been eliminated in this clinic.

There appears to be left a constant minimum death rate of probably close to two and one-half per cent for Group I cardiacs in pregnancy, due to causes other than recognizable heart failure—a death rate ten times higher than the death rate of normal women, as follows:

Just under one per cent of the cardiac patients have shown bacterial endocarditis.

Just under one per cent have had fatal pulmonary embolism. Cardiacs are either more apt to have embolism from venous thrombi or less able to survive them, or both. The incidence is many times higher than among normal women.

Five patients among the first 750 Group I cardiacs delivered died of puerperal sepsis. Only one of these deaths occurred in 600 individuals delivered from below (four-tenths of one per cent); four deaths occurred in 150 delivered by abdominal hysterotomy (two and seven-tenths per cent).

*How Shall We Deliver Our Cardiacs?*—Though early experience showed that emptying the uterus by abdominal hysterotomy did not cure the failing heart of a mother, it did show that even the worst cases survived the immediate strain of operation. For years we were afraid to let the worst cases go into labor. Improved medical care for the bad risks, a very high infant mortality if delivery occurs before the last two or three weeks, the drop in the load of pregnancy during the last few weeks, with the removal of the reasonable but false preconceived notions that the load increases steadily till term—all these have led us away from the temptation to deliver patients who are bad risks by abdominal hysterotomy before term. And in an attempt to lower the death rate from sepsis in the next sixteen years, we are now trying to avoid abdominal hysterotomy at term for cardiac indications alone. Shall we have thereby a greater number of deaths from heart failure provoked by labor? Only time can tell. Labor can produce heart failure in cardiacs, I have seen it do so—but the present feeling is that cardiacs, even sick cardiacs, stand labor surprisingly well.

#### REFERENCES

1. MacDonald, Angus: *The Bearings of Chronic Disease of the Heart Upon Pregnancy, Parturition, and Childbed*, London, 1878.
2. MacKenzie, Sir James: *Heart Disease and Pregnancy*, London, 1921.
3. Carr, F. B., and Hamilton, B. E.: *Five Hundred Women With Serious Heart Diseases Followed Through Pregnancy and Delivery*, *Am. J. Obst. & Gynec.* 26: 824, 1933.

## ORGANIC AND RELATIVE INSUFFICIENCY OF THE PULMONARY VALVE\*†

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IN THE past, many experienced clinicians and pathologists have considered pulmonary insufficiency as exceedingly rare and its clinical recognition unusually difficult.

Our experience in the wards and at the autopsy table of the Cincinnati General Hospital during the past few years has afforded convincing evidence that pulmonary insufficiency is relatively common and that the diagnosis in cases uncomplicated by other valvular lesions can usually be made during life if one bears the syndrome associated with this disorder in mind. Consequently we shall describe the clinical characteristics of certain of the cases we have had opportunity of observing during life and of proving at autopsy.

Probably the first reference in medical literature to a lesion of the pulmonary valve was made by Morgagni who presented in his treatise "*De Sedibus et Causis Morborum*," a case of Valsalva's of a young girl "who from birth had experienced great debility, and difficulty of respiration, and the surface of whose body was of a livid tint. The heart was small, and the relative state of the ventricles was reversed; for the right had the usual form of the left, and the left that which usually belongs to the opposite cavity. The capacity of the right auricle was twice that of the left; and its parietes were doubly fleshy. . . . The semilunar valves, at the origin of the pulmonary artery, were slightly ossified, and so united together that only a small foramen, sufficient to admit a lentil was left between them; and at this foramen, small and fleshy membranous productions existed, and were so placed as to act as valves, yielding to the blood as it proceeded from the heart, and resisting its return."<sup>1</sup>

The pathologists of this period apparently realized the infrequency of lesions of the pulmonary valve, as Corvisart is said to have stated that Morgagni was the only author who had observed this condition.

In 1832, James Hope<sup>2</sup> after an able description of aortic, mitral, and tricuspid valvular lesions remarked, "I have never seen the latter [pulmonic valves] diseased, but I have once found them incapable of closing the orifice in consequence of dilatation of the artery."

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†Read before The American Heart Association, Section for the Study of Cardiac Diseases, at Atlantic City, June 8, 1937.

Present day pathologists are in agreement that pulmonary valve lesions are uncommon, especially those of an acquired nature. In an exhaustive survey of the German literature, in 1931, Vellguth<sup>3</sup> concluded that valvular insufficiency of the pulmonary orifice was extraordinarily rare, and cited Finkelstein and Schultze, who found four cases each of pulmonary valve deficiency in 335 and 909 cases, respectively, of heart disease. Herrmann<sup>4</sup> found five cases in 4,776 autopsies at the Charity Hospital in New Orleans, all five of which were apparently rheumatic in origin. Of 24,000 consecutive admissions to the Johns Hopkins Hospital, Hirschfelder<sup>5</sup> found only three cases showing signs of pulmonary regurgitation.

Various classifications of pulmonary insufficiency have been suggested by different authors, but no uniform etiological grouping is as yet established. White states that the lesion may be associated with mitral stenosis; chronic failure of the left ventricle with pulmonary vascular congestion and hypertension; chronic lung disease giving rise to the same mechanical condition; chronic obliterative pulmonary endarteritis; congenital defects of the pulmonary valve giving rise to hypertension; perhaps wide patency of the ductus arteriosus and acute or chronic endocarditis of the pulmonary valve itself. Vaquez classifies the cases into organic and relative insufficiency.

Since the material at our disposal seems better adapted to this terminology, we have accordingly divided our cases into two groups:\*

- I. Organic Insufficiency: 1. Rheumatic
- 2. Bacterial
- 3. Syphilitic
- II. Relative Insufficiency: 1. Dilatation of the pulmonary artery secondary to pulmonary arteriosclerosis
- 2. Mitral stenosis

#### ORGANIC PULMONARY INSUFFICIENCY

##### 1. *Rheumatic Endocarditis of the Pulmonary Valve*

The occurrence of the rheumatic type of lesion is quite uncommon according to most authorities. Libman<sup>8</sup> in 1923 stated that in his series of cases up to that time the pulmonary valve "was not found affected in any definitely proved cases of rheumatic fever." Poynton and Schlesinger<sup>9</sup> in 1931 stated that "... it is exceptional to find vegetations on the pulmonary valve," though they added that "up to the present so little attention has been directed to lesions of the pulmonary valve in active rheumatism that their presence may have been overlooked." Thayer<sup>10</sup> encountered lesions of the pulmonary valve in one of 24 cases of rheumatic endocarditis.

\*No congenital lesions of the pulmonary valve were seen, probably owing in great measure to the fact that children are not admitted to the medical wards.

However, in 30 cases of rheumatic heart disease selected at random from the files of the Department of Pathology of the Cincinnati General Hospital lesions of the pulmonary valve were found in 14. In addition to microscopic lesions considered to be definitely rheumatic in these cases and similar to those described by Kugel and Epstein<sup>12</sup> there was gross deformity of the valve in three cases sufficient to produce a regurgitation at the orifice.

**CASE 1.—Summary:** *Rheumatic endocarditis affecting all valves.* R. W., a sixteen-year-old colored male, was admitted complaining of heart trouble. There was a history of St. Vitus' dance at the age of eight years. Dyspnea and palpitation developed following exertion and exposure to rain. Although the characteristic physical signs of a double mitral lesion were present, one examiner made the diagnosis of relative pulmonary insufficiency because of "a long diastolic murmur accompanied by a diastolic thrill present over the pulmonary area and transmitted down the sternum with a loud pulmonary second sound." A second examiner agreed because of the diastolic murmur in the third left interspace without peripheral signs of aortic insufficiency. Blood pressure was 105/70. Electrocardiogram showed right axis deviation and auricular fibrillation. X-ray films showed the heart to be enlarged in all directions, especially in the region of the left ventricle. Hemoglobin was 90 per cent.

Autopsy revealed gross stenosis in some degree of all four heart valves. Because of the thickening and contraction of the pulmonary valves and absence of peripheral signs of aortic insufficiency it seems logical to believe that the diastolic murmur may have been of pulmonary origin, although the aortic lesion cannot be entirely disregarded. Microscopically no active rheumatic lesions were found anywhere in the heart but there was subsiding activity throughout the substance of the scarred pulmonary valve.

**CASE 2.—Summary:** *Rheumatic endocarditis affecting all valves.* N. D., a thirty-two-year-old white woman, was admitted because of severe congestive heart failure. The patient stated that she had suffered with heart trouble since an attack of rheumatic fever at the age of eleven. She first complained of palpitation, then shortness of breath and cough. The patient was orthopneic and cyanotic; the pulse irregular, rate 110; blood pressure 128/70. The heart measured 4.5 by 15 cm. to percussion. A diastolic murmur was heard along the left sternal border.  $P_2$  was accentuated. A rough diastolic murmur was also heard below and outside the left sternal border. At the tricuspid area a soft systolic murmur was noted. The liver was enlarged and pulsated. No improvement followed treatment and the patient died forty-eight hours after admission. Electrocardiogram showed right axis deviation with negative  $T_2$  and  $T_3$ .

At autopsy acute verrucous endocarditis of the pulmonary valve was found. The verrucae were grossly visible. Microscopically, this case revealed typical rheumatic pancarditis with fresh rheumatic lesions of all of the heart valves.

**CASE 3.—Summary:** *Rheumatic endocarditis affecting all valves.* J. H., a twenty-five-year-old white laborer, had had dyspnea and ankle edema for four years before his death. The physical findings were characteristic of mitral stenosis and aortic insufficiency.

At autopsy rheumatic pancarditis was demonstrated, all valves being definitely affected. There was marked thickening and retraction of the cusps with stenosis of the pulmonary valve. Microscopically, the pulmonary valve revealed marked thickening, focal fibroblastic proliferation and scarring, with cellular infiltration and vascularization.

## 2. *Acute Bacterial Endocarditis of Pulmonary Valve*

Acute bacterial endocarditis of the pulmonary valve is stated to be of more common occurrence. In an analysis by Pitt<sup>12</sup> of 109 cases of pulmonary valve disease, 60 were due to infectious endocarditis. In the studies of Thayer<sup>10</sup> on bacterial endocarditis, the pulmonary valve was involved in the following proportions: Gonococcus, 6 of 21 cases; streptococcus, 2 of 34 cases; staphylococcus, 4 of 20 cases; pneumococcus, 1 of 40 cases.

CASE 4.—*Summary: Acute bacterial endocarditis of pulmonary valve (gonorrheal).* J. B., a colored male, aged twenty-eight years, entered the hospital because of acute intestinal obstruction which resulted from adhesions following repair of a gunshot wound of the abdomen. The patient had acquired an active gonorrheal urethritis a month before admission. Following a successful operation he ran a low grade fever for twenty-one days, then signs of pleurisy and consolidation of the left lung base developed. The following day soft systolic and loud diastolic murmurs were heard over the pulmonary area. The diastolic murmur was also audible but fainter in the second right interspace and along the sternal border.  $A_2$  was equal to  $P_2$ . Blood pressure was 120/70. X-ray film of the heart was negative. Electrocardiogram showed sinus tachycardia with low voltage of T-waves in Leads II and III; negative  $T_1$ . Two blood cultures were negative. The patient ran a down-hill course with symptoms and signs of sepsis and pulmonary infarction. Death occurred after ten weeks in the hospital. The clinical diagnosis was gonorrheal endocarditis of the pulmonary valve and possibly of the aortic valve.

At autopsy, bacterial endocarditis of all four valves was found. The pulmonary valve was so extensively involved that the pathologist recorded "pulmonary valvular insufficiency." Gram-negative and positive rods and streptococci were found in the post-mortem blood culture.

CASE 5.—*Summary: Acute bacterial endocarditis of pulmonary valve.* K. A., a fifty-five-year-old white female, developed weakness, diarrhea, loss of weight, and vomiting during two months preceding admission. Examination revealed pallor, marked purpura, and temperature 102° F. Systolic murmur over the sternum with split pulmonary second sound. Red blood cells numbered 2,000,000, hemoglobin 8 gm. Urine showed occasional red blood cell, albumin 4 plus. Blood culture was negative, blood urea 88. The patient died forty-eight hours after admission.

Autopsy showed the pulmonary valve leaflets to be completely destroyed by vegetations. The organism was not identified.

## 3. *Syphilis of the Pulmonary Artery*

The incidence of syphilis of the pulmonary artery is extremely uncommon. In 1933, Karsner<sup>13</sup> accepted 11 cases anatomically proved by reasonably liberal interpretation. Brenner<sup>14</sup> in 1935, stated that records of 65 cases of syphilis of the pulmonary artery were found in the literature but that in only 14 of these could the diagnosis be taken as being reasonably well established.

Syphilis may affect the pulmonary artery as a productive cicatricial lesion like the form common in the aorta, or it may be manifested by the formation of gummata. The proliferation type of lesion of the pulmonary artery shows essentially the same changes as those observed in syphilitic aortitis, and usually only the main trunk is involved.

CASE 6.—*Summary: Syphilitic arteritis, pulmonary artery and aorta.* P. F., a normally developed and poorly nourished married negroes of about forty-five years of age, was admitted to the Cincinnati General Hospital Nov. 1, 1931, because of congestive heart failure. For about three years prior to admission she had noticed occasional attacks of palpitation, effort dyspnea, infrequent attacks of nocturnal dyspnea, and slight swelling of the feet and ankles. Her general health had been good prior to three months before entering the hospital. There was no history suggesting congenital heart disease, rheumatic fever, or syphilis. Examination revealed orthopnea, cyanosis, and dependent edema extending to about the level of the umbilicus. The cervical veins were engorged and pulsating. The pulps were equal and reacted to light. A tracheal tug was present and visible pulsations were noted in the episternal notch. The bony framework of the chest was prominent and the apex beat was visible in the sixth left intercostal space about 14 cm. from the mid-sternal line. In the second and third interspaces on the left there was a visible and forceful pulsation extending 4 to 6 cm. to the left of the midsternal line. No abnormal pulsations were present to the right of the sternum. Over the pulmonic area, in the region of the visible pulsation, a harsh systolic murmur and a blowing diastolic murmur were of maximal intensity. Over the aortic area and at the apex systolic and diastolic murmurs were audible but of less intensity than the murmurs over the second left interspace. The cardiac rate was 40 at the apex and at the wrists. The rhythm was irregular. On the right the blood pressure was 142/89, on the left 182/90. No capillary pulsation was seen and the pulse was not of the Corrigan type. Duroziez's sign was absent. The heart measured 16.5 cm. in the fifth interspace. Congestive râles were present over both bases, and the firm, tender liver edge was easily palpable 3 fingerbreadths below the costal margin. The remainder of the examination was not remarkable except for dependent edema. Blood Wassermann reaction was strongly positive. Red blood cells were 4,500,000, hemoglobin was 80 per cent, white blood cells numbered 6,500. Electrocardiogram showed right axis deviation; complete A-V dissociation; T-waves of low voltage in all leads. X-ray films showed the heart to be markedly enlarged in all directions. The aorta was enlarged but showed no aneurysmal dilatation. On the left a large shadow was superimposed over the aorta in the region of the pulmonary artery which Dr. Hugo Roesler\* of Philadelphia identified as an aneurysm of the pulmonary artery (Fig. 1). The last admission was necessitated by extreme dyspnea and precordial pain and the heart sounds became weak, the respirations slow and the patient died quietly.

Anatomical diagnosis: Syphilitic pulmonary arteritis with dilatation of the pulmonary artery (pulmonary valve 100 mm. at orifice, aortic valve 85 mm. at orifice); syphilitic aortitis (clinically aortic and pulmonary insufficiency); syphilitic cirrhosis of the liver; thickening of the pulmonary and aortic valves; cardiac hypertrophy (900 gm.).

#### RELATIVE PULMONARY INSUFFICIENCY

Relative insufficiency of the pulmonary valves is most frequently secondary to increased intrapulmonary pressure secondary to mitral stenosis. Such insufficiency may be permanent or temporary. In either event the resulting diastolic murmur is called the Graham Steele murmur.

Pulmonary arteriosclerosis may likewise be associated with increase in intrapulmonary pressure, and relative pulmonary insufficiency.

\*As far as we can ascertain Dr. Roesler's diagnosis of aneurysm of the pulmonary artery is the first correct diagnosis of this condition before autopsy.

The incidence of pulmonary arteriosclerosis is considered to be approximately that of systemic arteriosclerosis though usually the process is not so severe. This is the type which is part of the picture of generalized vascular atherosclerosis and which does not cause any obvious harmful results. If, however, the extent or situation of the sclerosis causes obstruction to the circulation through the lungs, dilatation and hypertrophy of the right heart will occur, with subsequent signs and symptoms of myocardial failure. This type is known as primary pulmonary arteriosclerosis, or arteriolosclerosis, and is considered to be a rare condition. MacCallum<sup>16</sup> found one case in 12,000 autopsies. According to Brenner<sup>14</sup> there are 16 cases in the literature which can be accepted as fulfilling the criteria for diagnosis.

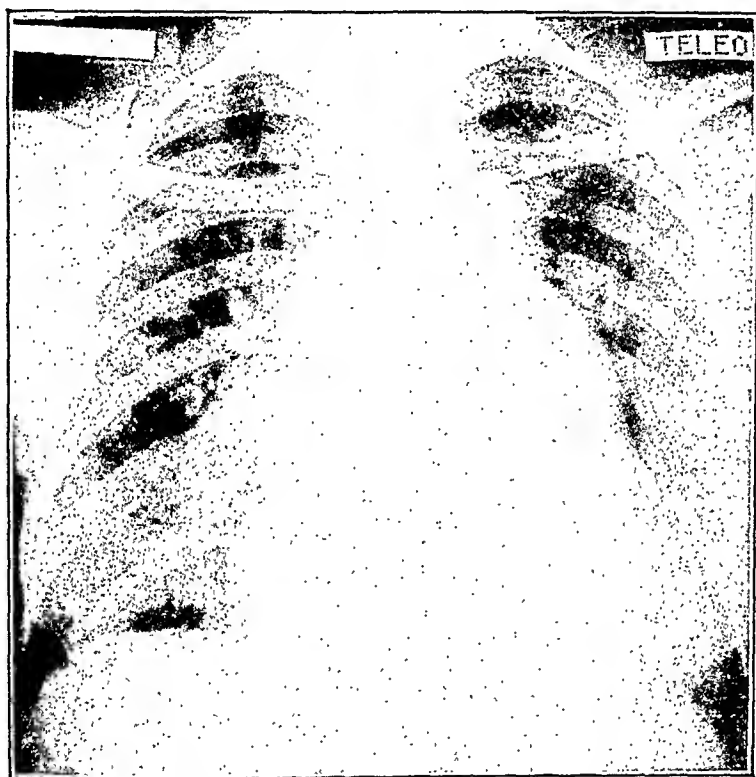


Fig. 1.—Case 6. Teleroentgenogram showing prominent pulmonary conus and branches of pulmonary artery, dilated aorta, and cardiac enlargement.

Karsner<sup>15</sup> divides pulmonary arteriosclerosis into primary, in which the arterioles are involved and in which marked hypertrophy of the right heart is present without demonstrable mechanical or functional cause on gross examination, and secondary, in which the sclerosis is subsequent to chronic diseases of the heart, lung, and pleura. The lesions of secondary pulmonary sclerosis appear principally in the main stems and larger branches of the pulmonary artery.

### 1. *Pulmonary Arteriosclerosis*

CASE 7.—*Summary: Systemic and pulmonary arteriosclerosis and arteriolosclerosis.* L. H., a forty-four-year-old white housewife, was admitted to the Cincinnati General Hospital in March, 1935 with the complaint of extreme shortness of breath. Effort



dyspnea occurred for the first time in 1931. There was the history of growing pains in childhood, and polyarticular arthritis eight years before, following the birth of her tenth child.

The significant findings were; temperature 99.2, pulse 95, respirations 25, blood pressure 160/120, orthopnea, moderate cyanosis of tongue, lips, fingers, and skin. The lungs showed many medium moist râles at the bases. The heart width measured 18.5 cm., the thoracic width being 31. The pulse was slightly irregular at times (extrasystoles). One examiner reported the classical signs of moderately advanced mitral stenosis at the apex because of a rumbling diastolic murmur at the apex. This murmur was inconstant.  $P_2$  was louder than  $A_2$  and was split at the aortic area. None of the peripheral signs of aortic insufficiency such as Duroziez's sign, capillary pulsation, or pistol-shot sounds were present. X-ray films showed "great enlargement of the left auricle and pulmonary conus. Pulmonary artery is particularly visible. Chronic infiltrative changes in both hilar regions" (Fig. 2). Fluoroscopy



Fig. 2.—Case 7. Teleroentgenogram showing marked prominence of pulmonary conus and cardiac enlargement.

showed the violent pulsations of the branches of the pulmonary artery in the hilum characteristic of pulmonary valvular insufficiency. Electrocardiogram showed right axis deviation; diphasic  $T_1$  and  $T_2$ . Red blood cells numbered 5,800,000, hemoglobin was 90 per cent. The patient improved rapidly with *digitalis* and rest and was sent home. Subsequently she was readmitted on three occasions because of dyspnea and edema. On the last admission she died suddenly and unexpectedly. The clinical diagnosis was "pulmonary valvular insufficiency, probably organic."

Autopsy: Heart weight 575 gm. Pulmonary orifice dilated, measuring 95 mm., the aortic valve measuring 70 mm. Myocardium of the right ventricle greatly hypertrophied. Marked atherosclerosis of the pulmonary artery. Thrombi present in both branches of the pulmonary artery. The failure of the right ventricle in this case may be attributed to a combination of factors, chronic failure of the left ventricle with pulmonary congestion and an increased right ventricular strain, very possibly associated with pulmonary hypertension.

CASE 8.—*Summary: Primary pulmonary arteriosclerosis.* P. O'H., a forty-two-year-old white male, was admitted with a productive cough of ten years' duration. There had been dyspnea on exertion for six years. The patient had been deaf and dumb since birth. Examination showed cyanosis, moderate cardiac enlargement, systolic murmurs, and thrill maximum in third left interspace.  $P_2$  was accentuated. Electrocardiogram showed right axis deviation. X-ray films showed prominence of the pulmonary conus with cardiac enlargement (Fig. 3). Red blood cells numbered 4,500,000, hemoglobin was 80 per cent (Sahli). Clinical diagnosis: Congenital pulmonic stenosis; lobar pneumonia.

Autopsy: Unresolved lobar pneumonia with empyema; pulmonary arteriosclerosis with right ventricular hypertrophy and dilatation. The pulmonary valve orifice measured 115 mm., the aortic 60 mm.

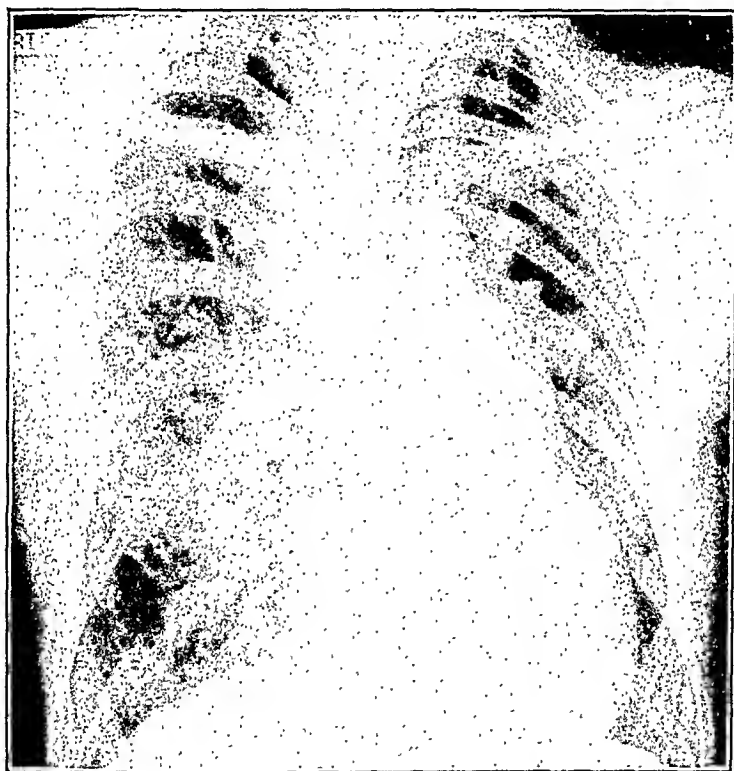


Fig. 3.—Case 8. Teleroentgenogram showing prominent pulmonary conus and dilatation of branches of pulmonary artery in right hilum. There is moderate scoliosis.

## 2. Mitral Stenosis With Graham Steele Murmur

CASE 9.—*Summary: Mitral stenosis with dilatation of pulmonary artery.* R. D., a forty-six-year-old white male, gave the history of dyspnea, cough and weakness followed by edema of ankles over a period of five years. There was moderate cardiac enlargement and the characteristic signs of mitral stenosis. A long, blowing diastolic murmur was heard along the left sternal border, maximal in the third to fourth interspace. Blood pressure was 100/80. There was absence of peripheral signs of aortic valvulitis. Electrocardiogram showed right axis deviation. X-ray films showed straight left cardiac silhouette and enlargement of the right heart. Clinical Diagnosis: Mitral stenosis with relative pulmonary insufficiency (Graham Steele murmur).

Autopsy: Cardiac hypertrophy, especially of the right heart; mitral and aortic stenosis; dilatation of pulmonary artery and pulmonic orifice (90 mm.).

## SUMMARY

The pathological and clinical features of 9 cases of pulmonary insufficiency have been presented. The lesion is ordinarily considered very unusual, yet 4 cases have been observed in the Cincinnati General Hospital within the past year.

The etiological factors found in this series of cases were: Rheumatic fever, bacterial endocarditis, pulmonary arteriolosclerosis; systemic and probably pulmonary hypertension; syphilitic pulmonary arteritis, and mitral stenosis.

In all the cases caused by rheumatic fever there were clinical signs of involvement of more than one valve. Lesions of all four valves were found at autopsy in each case. The presence of multiple valvular lesions makes the diagnosis of pulmonary insufficiency very difficult.

There were no symptoms in our cases characteristic of pulmonary insufficiency per se. The symptoms depended upon the existing disease process and the degree of myocardial insufficiency.

The clinical features characterizing pulmonary insufficiency were a diastolic murmur in the second left interspace transmitted towards the axilla, accentuation of the pulmonary second sound, prominence of the pulmonary conus, marked pulsation of the hilum vessels, and right axis deviation of the electrocardiogram.

## REFERENCES

1. Morgagni, J. B.: *The Seats and Causes of Disease*, Translation of William Cooke, Philadelphia, 1824, Carey and Lea.
2. Hope, James: *A Treatise on the Diseases of the Heart and Great Vessels*, London, 1832, William Kidd, p. 318.
3. Vellguth, H.: *Zur Pathologie der Pulmonalinsuffizienz*, Beitr. z. path. Anat. u. z. allg. Path. 86: 517, 1931.
4. Hermann, George: *Oxford Medicine*, Vol. II, Part II, 492.
5. Hirschfelder, A. D.: *Diseases of the Heart and Aorta*, Philadelphia, 1910, Lippincott, p. 390.
6. White, P. D.: *Heart Disease*, New York, 1937, The Macmillan Company, p. 456.
7. Vaquez, Henri: *Diseases of the Heart*, Philadelphia, 1924, W. B. Saunders Company, p. 402.
8. Libman, E.: *Characterization of Various Forms of Endocarditis*, J. A. M. A. 80: 813, 1923.
9. Poynton, F. J. and Schlesinger, B.: *Recent Advances in Rheumatism*, Philadelphia, 1931, P. Blakiston's Son & Co.
10. Thayer, W. S.: *Studies on Bacterial Endocarditis*, 1926.
11. Kugel, M. A., and Epstein, E. Z.: *Lesions in the Pulmonary Artery and Valve Associated With Rheumatic Cardiac Disease*, Arch. Path. 6: 247, 1928.
12. Pitt, G. Newton: Quoted by H. B. Allyn: *Insufficiency of the Pulmonary Valve*, Am. J. M. Sc. 146: 541, 1913.
13. Karsner, H. T.: *Productive-Cicatricial Syphilitic Disease of the Pulmonary Artery*, Arch. Int. Med. 51: 367, 1933.
14. Brenner, O.: *Pathology of the Vessels of the Pulmonary Circulation*, Arch. Int. Med. 56: 211, 1935.
15. Karsner, H. T.: *Arteriosclerosis*, edited by Cowdry, New York, 1933, The Macmillan Company, p. 457.
16. MacCallum, W. G.: *Obliterative Pulmonary Arteriolosclerosis*, Bull. Johns Hopkins Hosp. 49: 37, 1931.

## AN UNUSUAL CASE OF AURICULAR PARASYSTOLE SHOWING "EXIT" BLOCK\*

L. N. KATZ, M.D., J. L. ESCHELBACHER, M.D., AND S. STRAUSS, M.D., IN  
COLLABORATION WITH S. H. ROBERTSON, M.D., AND H. BINSWANGER, M.D.  
CHICAGO, ILL.

CONSIDERABLE controversy has existed regarding the mechanism responsible for frequent ectopic premature beats (Wenckebach and Winterberg,<sup>1</sup> Lewis,<sup>2</sup> and Rothberger<sup>3</sup>). While the idea of occasional haphazard awakening of dormant ectopic pacemakers has been advocated and the view of re-entry has been promulgated to explain fixed coupling, the Viennese school led by Rothberger has put forth the concept that many forms of premature systoles and paroxysmal tachycardias are due to the constant activity of a secondary pacemaker (or pacemakers) competing with the sinus pacemaker for control of the heart. This is the fundamental concept of parasystole. In its simplest form as developed by Kaufmann and Rothberger,<sup>4</sup> parasystole presupposes the formation of rhythmic stimuli at an abnormal focus at a frequency measured by the shortest time interval between two ectopic beats. The longer intervals (during which sinus beats intervene between the ectopic beats) are multiples of the shorter time intervals and arise because of interference by the sinus impulse. Activation of the heart by the ectopic impulse when it falls in the refractory period of the heart follows stimulation by the sinus. The continuous activity of the secondary pacemaker, contrary to ordinary conditions, and the failure of the sinus impulse to obliterate or affect it, demand the existence of an "entrance" or "protection" block (*Eintritts* or *Schützblockierung*) around the ectopic pacemaker. In some instances an inherent rate of the ectopic pacemaker faster than the sinus rate has been assumed to explain the timing of ectopic beats, and this has demanded the view that some of the impulses from the ectopic pacemaker are blocked, not because the entire chamber (auricle or ventricle) is in the refractory phase (interference), but because of a localized block, a so-called "exit" block (*Austrittsblockierung*), preventing the impulse from leaving the pacemaker.

While the ideas of interference and protection block have ample evidence to support them (cf. case reports<sup>4, 5, 6, 7, 8, 9</sup>), no direct clear evidence of exit block exists, as the cases cited by Kaufmann and Rothberger<sup>4</sup> to support this view have been criticized by Singer and Winterberg.<sup>5</sup>

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Aided by the A. D. Nast Fund for Cardiac Research.

Recently we have seen a patient who has had over a period of years sinus bradycardia, intraventricular block, multiple active ectopic pacemakers of the auricle and ventricle, and attacks of auricular flutter and paroxysmal tachycardia. On one occasion the electrocardiogram clearly demonstrated exit block. We are therefore presenting the case report with the pertinent electrocardiograms and tabular summaries of our measurements in order to lend support to the existence of parasystole with exit block.

### CASE REPORT

The patient was first seen by one of us (H. B.) in association with Dr. Sol Strouse in the fall of 1926. He was fifty-seven years of age at that time. His complaints at that time were of indefinite pains in the abdomen which were considered to be genitourinary in origin. He had had tuberculosis in his early youth. He showed evidence of arteriosclerosis with cardiac enlargement, a slow pulse, and a blood pressure of 175/100. In the spring of 1927 he had pus cells in his urine and later developed uremia. He was operated upon; an infected patent urachus was removed and a prostatectomy was performed. His recovery was uneventful. His blood pressure fell to 140/80. In the fall of 1928 on x-ray examination a duodenal ulcer was noted. In the spring of 1930 he had an anemia due to a hemorrhage from this.

In the summer of 1932, he returned complaining for the first time of pain in the chest (1 cm. to the left of the heart's apex); this spot was also tender. No change was noted in the heart findings; the x-ray examination showed a dilated aorta. An electrocardiogram taken at this time showed intraventricular block of the common bundle-branch type with frequent ventricular and auricular extrasystoles from multiple foci. (This will be discussed in detail below.) The patient stated that irregularity of his heart had been noted as far back as 1899. In 1933 he had trouble with hemorrhoids and complained also of precordial and abdominal distress. His heart had been slow and irregular whenever he was examined. During this period treatment was directed toward the relief of the duodenal ulcer.

In 1934 his cardiac symptoms came to the fore, and his ulcer symptoms receded. During the winter, he had a flare-up of his pulmonary tuberculosis with fever, rales in the right infrascapular region, and tubercle bacilli in the sputum. He went to a spa over the winter and returned in the spring of 1935 much improved. His cardiac examination was unchanged. During a visit to New York in May, his cough returned. In August he had a sudden attack of shortness of breath and felt very ill. He was seen at his home by one of us (S. H. R.), who found the pulse rapid and rales in the upper chest bilaterally. The pulse quickly returned to its normal rate. The patient was kept in bed for several days.

In the fall of 1935 another attack occurred, and the patient was seen by two of us (S. S. and H. B.). He had cyanosis, dyspnea, and rales in the infrascapular regions and at both bases; his pulse was irregular and at times bigeminal. He recovered from this attack on rest in bed. He had several electrocardiograms taken afterward which were similar in general character to the one taken in 1932, except in one there was a paroxysm of ventricular extrasystoles.

In the spring of 1936 he had another "heart" attack with tachycardia and dyspnea, from which he gradually recovered with bed rest, morphine, and digitalis. The four-lead electrocardiogram taken at this time had the chief clue to the mechanism of his irregularity. From this time on he was under the care of one of us (S. S.). A new attack of tachycardia and heart failure was induced in August, 1936, by excitement. On bed rest, morphine, and large doses of digitalis his condition improved. In September he had an attack of tachycardia, the pulse going to 122-144

(his normal rate being 44-60. At the slow rate of 44, the heart usually showed a bigeminy). It stayed at this rapid rate for several days. Quinidine 3 gr. every two hours was given. At the same time a source of great apprehension was removed, and the pulse became slow within a few hours. During the tachycardia, carotid sinus pressure and breath holding both caused transitory slowing. The mechanism appeared to be auricular flutter. After that the patient had several attacks of paroxysmal tachycardia; these were controlled by quinidine. An electrocardiogram taken during one showed the mechanism to be auricular flutter with 2:1 conduction. A long four-lead electrocardiogram containing 425 ventricular beats was taken at this period.

On physical examination during the winter of 1936, the left border of the heart was found to be 15 cm. from the midsternal line, the right, 4 cm. His cardiothoracic ratio in the x-ray film was 16/31. He had many calcified tuberculous nodules throughout both lungs. A blowing systolic murmur was heard at the apex. His blood pressure was 130-180/80. The liver was palpable 2 or 3 fingerbreadths below the costal margin.

The diagnosis at this time made by one of us (S. S.) was: (1) arteriosclerotic heart disease (coronary sclerosis); (2) cardiac hypertrophy; (3) extrasystoles and auricular flutter (neurogenic?); (4) healed pulmonary tuberculosis; and (5) healed duodenal ulcer.

The patient went to California for the winter. There he acquired an embolus in his left brachial artery, his left hand and fingers became numb, and he had pain in this arm above the elbow. No radial or cubital pulse was felt on this side. A short while later his cardiac symptoms and signs recurred in severe form; coma developed; and death occurred within several days. No autopsy was obtained.

#### ANALYSIS AND INTERPRETATION OF ELECTROCARDIOGRAMS

The electrocardiograms taken on May 20, 1936, and on July 7, 1932, are shown in Figs. 1 and 2, respectively, and Figs. 3 to 8 show portions of the long four-lead electrocardiogram taken on Oct. 26, 1936.

1. *Electrocardiogram Taken May 20, 1936.*—The most significant electrocardiogram is the one shown in Fig. 1, since inspection of this record led one of us (L. N. K.) to suspect the presence of parasystole with exit block, and measurements confirmed this impression. It will be seen that in each lead there are two types of P-waves, those marked *P* and those marked (*P*). (The nature of  $P_{11}$  in Lead I is in doubt; it may be a fusion form.) The QRS complexes are all alike and show the typical characteristics of intraventricular block of the common bundle-branch type.

Accurate measurements were made of all the P-P intervals, and the results are shown in Fig. 1 and are assembled in Table I. It is apparent that there are four kinds of P-P intervals: viz. (1) P-P, (2) (P)-P, (3) (P)-(P) and (4) P-(P); these were separated from each other in summarizing the measurements.

It was soon apparent that the P-P intervals, of which there were eight (Table II), were all equal in duration (1.28 sec.) except one which was 0.04 sec. less. It was also obvious that the (P)-P intervals were equal in duration or a trifle longer than the P-P intervals; viz. 1.24 to 1.36 sec. (Table III). It was, therefore, concluded that the auricular waves marked *P* were sinus in origin, that the auricular waves marked (*P*) were



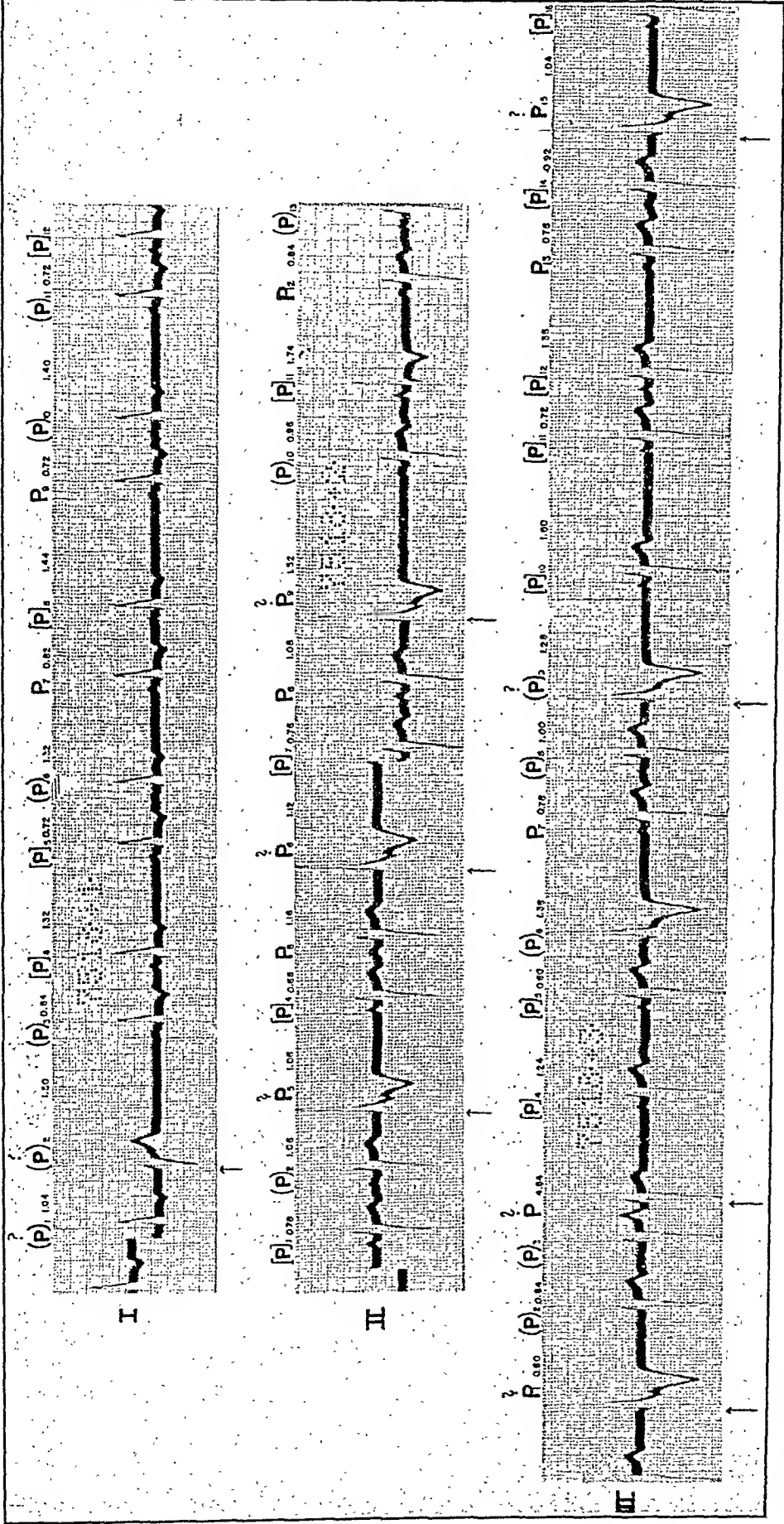


Fig. 2.—Electrocardiogram (three-lead) taken on this patient on July 7, 1932, showing three parasystolic rhythms indicated by P, (P) and (P). The interauricular intervals are marked as in Fig. 1. The P-waves with ? above cannot be identified as to origin. Below each lead the ventricular ectopic beats are indicated by upright arrows. Discussed in text.



TABLE I  
INTERVAL BETWEEN ALL P-WAVES (FIG. 1)

| LEAD I                           |                             | LEAD II                          |                             | LEAD III                         |                             | LEAD IV                          |                             |
|----------------------------------|-----------------------------|----------------------------------|-----------------------------|----------------------------------|-----------------------------|----------------------------------|-----------------------------|
| IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. | IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. | IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. | IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. |
| P <sub>1</sub> -P <sub>2</sub>   | 0.88                        | P <sub>1</sub> -P <sub>2</sub>   | 0.88                        | P <sub>1</sub> -P <sub>2</sub>   | 1.28                        | P <sub>1</sub> -P <sub>2</sub>   | 1.04                        |
| P <sub>2</sub> -P <sub>3</sub>   | 1.00                        | P <sub>2</sub> -P <sub>3</sub>   | 1.32                        | P <sub>2</sub> -P <sub>3</sub>   | 0.48                        | P <sub>2</sub> -P <sub>3</sub>   | 1.12                        |
| P <sub>3</sub> -P <sub>4</sub>   | 1.00                        | P <sub>3</sub> -P <sub>4</sub>   | 0.46                        | P <sub>3</sub> -P <sub>4</sub>   | 1.00                        | P <sub>3</sub> -P <sub>4</sub>   | 0.60                        |
| P <sub>4</sub> -P <sub>5</sub>   | 1.12                        | P <sub>4</sub> -P <sub>5</sub>   | 1.34                        | P <sub>4</sub> -P <sub>5</sub>   | 0.80                        | P <sub>4</sub> -P <sub>5</sub>   | 1.24                        |
| P <sub>5</sub> -P <sub>6</sub>   | 0.76                        | P <sub>5</sub> -P <sub>6</sub>   | 0.96                        | P <sub>5</sub> -P <sub>6</sub>   | 1.28                        | P <sub>5</sub> -P <sub>6</sub>   | 1.20                        |
| P <sub>6</sub> -P <sub>7</sub>   | 1.24                        | P <sub>6</sub> -P <sub>7</sub>   | 0.80                        | P <sub>6</sub> -P <sub>7</sub>   | 1.24                        | P <sub>6</sub> -P <sub>7</sub>   | 1.28                        |
| P <sub>7</sub> -P <sub>8</sub>   | 0.80                        | P <sub>7</sub> -P <sub>8</sub>   | 1.28                        | P <sub>7</sub> -P <sub>8</sub>   | 0.60                        | P <sub>7</sub> -P <sub>8</sub>   | 0.80                        |
| P <sub>8</sub> -P <sub>9</sub>   | 1.32                        | P <sub>8</sub> -P <sub>9</sub>   | 1.28                        | P <sub>8</sub> -P <sub>9</sub>   | 1.36                        | P <sub>8</sub> -P <sub>9</sub>   | 1.28                        |
| P <sub>9</sub> -P <sub>10</sub>  | 1.28                        | P <sub>9</sub> -P <sub>10</sub>  | 1.28                        | P <sub>9</sub> -P <sub>10</sub>  | 0.80                        | P <sub>9</sub> -P <sub>10</sub>  | 1.28                        |
| P <sub>10</sub> -P <sub>11</sub> | 1.28                        | P <sub>10</sub> -P <sub>11</sub> | 0.72                        | P <sub>10</sub> -P <sub>11</sub> | 1.28                        | P <sub>10</sub> -P <sub>11</sub> | 1.28                        |
| P <sub>11</sub> -P <sub>12</sub> | 0.84                        | P <sub>11</sub> -P <sub>12</sub> | 1.28                        | P <sub>11</sub> -P <sub>12</sub> | 1.16                        | P <sub>11</sub> -P <sub>12</sub> | 1.12                        |
| P <sub>12</sub> -P <sub>13</sub> | 1.16                        |                                  |                             | P <sub>12</sub> -P <sub>13</sub> | 1.28                        | P <sub>12</sub> -P <sub>13</sub> | 0.64                        |
| P <sub>13</sub> -P <sub>14</sub> | 0.84                        |                                  |                             | P <sub>13</sub> -P <sub>14</sub> | 0.76                        | P <sub>13</sub> -P <sub>14</sub> | 1.28                        |
| P <sub>14</sub> -P <sub>15</sub> | 1.32                        |                                  |                             | P <sub>14</sub> -P <sub>15</sub> | 1.28                        | P <sub>14</sub> -P <sub>15</sub> | 1.28                        |
| P <sub>15</sub> -P <sub>16</sub> | 1.28                        |                                  |                             | P <sub>15</sub> -P <sub>16</sub> | 0.52                        | P <sub>15</sub> -P <sub>16</sub> | 0.76                        |
| P <sub>16</sub> -P <sub>17</sub> | 0.92                        |                                  |                             | P <sub>16</sub> -P <sub>17</sub> | 1.32                        | P <sub>16</sub> -P <sub>17</sub> | 1.36                        |
|                                  |                             |                                  |                             | P <sub>17</sub> -P <sub>18</sub> | 0.76                        |                                  |                             |
|                                  |                             |                                  |                             | P <sub>18</sub> -P <sub>19</sub> | 1.28                        |                                  |                             |

TABLE II  
P-P INTERVALS (FIG. 1)

| LEAD I                           |                             | LEAD II                         |                             | LEAD III                       |                             | LEAD IV                          |                             |
|----------------------------------|-----------------------------|---------------------------------|-----------------------------|--------------------------------|-----------------------------|----------------------------------|-----------------------------|
| IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. | IN-<br>Terval                   | DURA-<br>TION<br>IN<br>SEC. | IN-<br>Terval                  | DURA-<br>TION<br>IN<br>SEC. | IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. |
| P <sub>9</sub> -P <sub>10</sub>  | 1.28                        | P <sub>8</sub> -P <sub>9</sub>  | 1.28                        | P <sub>6</sub> -P <sub>7</sub> | 1.24                        | P <sub>9</sub> -P <sub>10</sub>  | 1.28                        |
| P <sub>15</sub> -P <sub>16</sub> | 1.28                        | P <sub>9</sub> -P <sub>10</sub> | 1.28                        |                                |                             | P <sub>10</sub> -P <sub>11</sub> | 1.28                        |
|                                  |                             |                                 |                             |                                |                             | P <sub>11</sub> -P <sub>12</sub> | 1.28                        |

1.24 = 48 per minute.  
1.28 = 47 per minute.

TABLE III  
(P)-P INTERVALS (FIG. 1)

| LEAD I                           |                             | LEAD II                          |                             | LEAD III                         |                             | LEAD IV                          |                             |
|----------------------------------|-----------------------------|----------------------------------|-----------------------------|----------------------------------|-----------------------------|----------------------------------|-----------------------------|
| IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. | IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. | IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. | IN-<br>Terval                    | DURA-<br>TION<br>IN<br>SEC. |
| P <sub>8</sub> -P <sub>9</sub>   | 1.32                        | P <sub>2</sub> -P <sub>3</sub>   | 1.32                        | P <sub>1</sub> -P <sub>2</sub>   | 1.28                        | P <sub>1</sub> -P <sub>2</sub>   | 1.24                        |
| P <sub>11</sub> -P <sub>12</sub> | 1.32                        | P <sub>4</sub> -P <sub>5</sub>   | 1.34                        | P <sub>2</sub> -P <sub>3</sub>   | 1.28                        | P <sub>4</sub> -P <sub>5</sub>   | 1.28                        |
|                                  |                             | P <sub>7</sub> -P <sub>8</sub>   | 1.28                        | P <sub>5</sub> -P <sub>6</sub>   | 1.36                        | P <sub>8</sub> -P <sub>9</sub>   | 1.28                        |
|                                  |                             | P <sub>11</sub> -P <sub>12</sub> | 1.28                        | P <sub>10</sub> -P <sub>11</sub> | 1.28                        | P <sub>11</sub> -P <sub>12</sub> | 1.28                        |
|                                  |                             |                                  |                             | P <sub>12</sub> -P <sub>13</sub> | 1.28                        | P <sub>10</sub> -P <sub>11</sub> | 1.28                        |
|                                  |                             |                                  |                             | P <sub>14</sub> -P <sub>15</sub> | 1.28                        | P <sub>11</sub> -P <sub>12</sub> | 1.36                        |
|                                  |                             |                                  |                             | P <sub>16</sub> -P <sub>17</sub> | 1.28                        |                                  |                             |
|                                  |                             |                                  |                             | P <sub>18</sub> -P <sub>19</sub> | 1.28                        |                                  |                             |

1.24 = 48 per min.  
1.28 = 47 per min.  
1.32 = 46 per min.  
1.34 = 45 per min.  
1.36 = 44 per min.

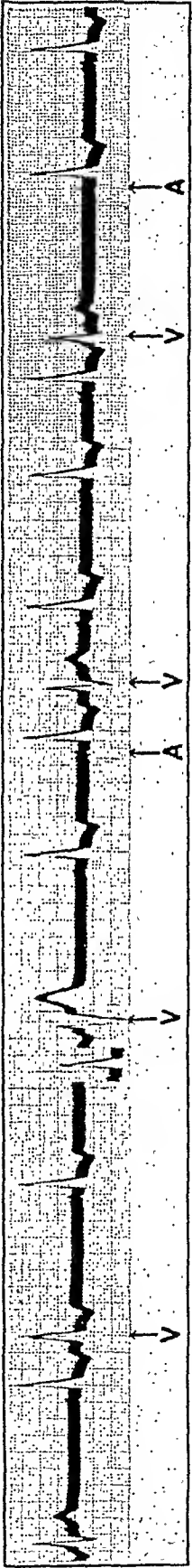


Fig. 3.—Portion of Lead I taken on Oct. 26, 1936, to show two auricular and four ventricular ectopic pacemakers identified respectively by upright arrows marked A and V. Discussed in text.

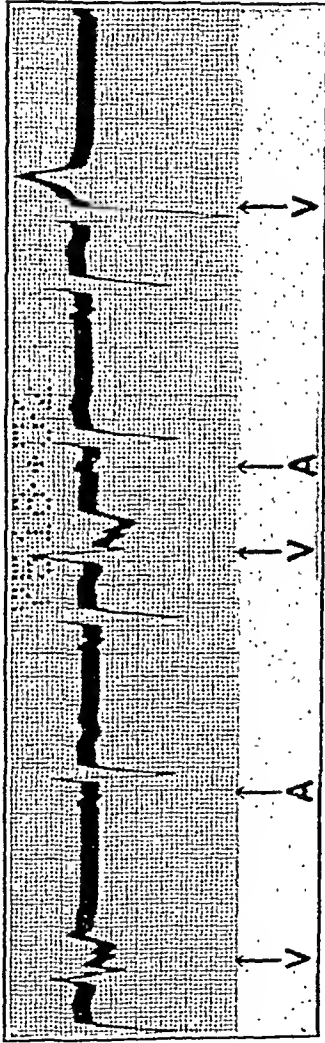


Fig. 4.

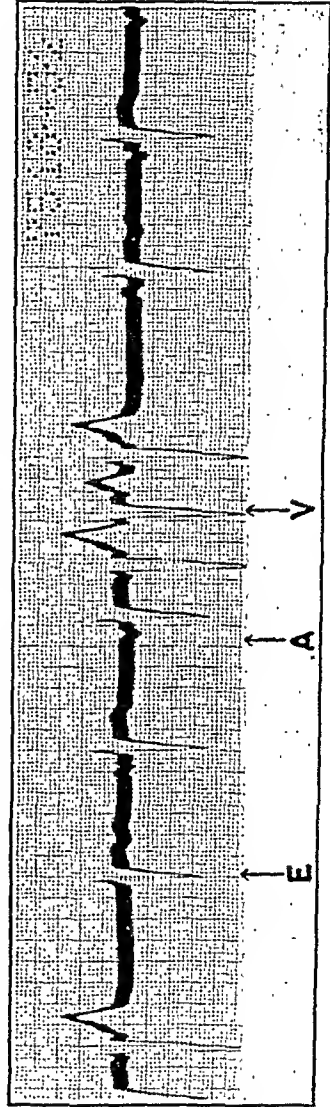


Fig. 5.

Figs. 4 and 5.—Portions of Lead II taken on Oct. 26, 1936, to show three auricular and four ventricular ectopic pacemakers identified as in Fig. 3. E indicates a nodal escape. Discussed in text.

from a focus close to the sinus node, and that the (P)-P intervals were similar to the interval following an auricular premature systole arising close to the sinus node. No correlation could be made in regard to the P-(P) intervals.

The (P)-(P) intervals (Table IV), it will be seen, are multiples of a cycle length equal to 0.16 sec.  $\pm$  0.01, which is equivalent to a parasystolic rhythm with a rate of 375 per minute (which incidentally was the auricular flutter rate found during an attack). There is, therefore, an exit block giving rise to a ratio of total impulses over those conducted of from 4:1 to 8:1.

TABLE IV  
(P)-(P) INTERVALS (Fig. 1)

| LEAD I                           |                     |   |   | LEAD II                          |                     |   |   |
|----------------------------------|---------------------|---|---|----------------------------------|---------------------|---|---|
| INTERVAL                         | DURATION<br>IN SEC. | RATIO OF CONDUCTED<br>BEATS OF PARA-<br>SYSTOLIC RHYTHM | CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM | INTERVAL                         | DURATION<br>IN SEC. | RATIO OF CONDUCTED<br>BEATS OF PARA-<br>SYSTOLIC RHYTHM | CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM |
| P <sub>2</sub> -P <sub>3</sub>   | 1.00                | 6:1   | 0.17                                      | P <sub>6</sub> -P <sub>7</sub>   | 0.80                | 5:1   | 0.16                                      |
| P <sub>3</sub> -P <sub>4</sub>   | 1.00                | 6:1   | 0.17                                      |                                  |                     |   |   |
| P <sub>4</sub> -P <sub>5</sub>   | 1.12                | 7:1   | 0.16                                      |                                  |                     |   |   |
| P <sub>5</sub> -P <sub>6</sub>   | 0.76                | 5:1   | 0.15                                      |                                  |                     |   |   |
| P <sub>6</sub> -P <sub>7</sub>   | 1.24                | 8:1   | 0.16                                      |                                  |                     |   |   |
| P <sub>7</sub> -P <sub>8</sub>   | 0.80                | 5:1   | 0.16                                      |                                  |                     |   |   |
| P <sub>11</sub> -P <sub>12</sub> | 0.84                | 5:1   | 0.17                                      |                                  |                     |   |   |
| P <sub>12</sub> -P <sub>13</sub> | 1.16                | 7:1   | 0.17                                      |                                  |                     |   |   |
| P <sub>13</sub> -P <sub>14</sub> | 0.84                | 5:1   | 0.17                                      |                                  |                     |   |   |
| LEAD III                         |                     |   |   | LEAD IV                          |                     |   |   |
| P <sub>2</sub> -P <sub>4</sub>   | 1.00                | 6:1   | 0.17                                      | P <sub>1</sub> -P <sub>2</sub>   | 1.04                | 6:1   | 0.17                                      |
| P <sub>4</sub> -P <sub>5</sub>   | 0.80                | 5:1   | 0.16                                      | P <sub>2</sub> -P <sub>3</sub>   | 1.12                | 7:1   | 0.16                                      |
|                                  |                     |   |   | P <sub>3</sub> -P <sub>4</sub>   | 0.60                | 4:1   | 0.15                                      |
|                                  |                     |   |   | P <sub>12</sub> -P <sub>13</sub> | 0.64                | 4:1   | 0.16                                      |

0.15 = 400 beats per minute.

0.16 = 375 beats per minute.

0.17 = 353 beats per minute.

In brief, to recapitulate, the auricular waves marked (P) in Fig. 1 are thus sinus in origin, and those marked P are ectopic. The fact that the calculated cycle length for the parasystolic rhythm varies  $\pm$  0.01 sec. is not surprising on biological grounds and because the error in measuring the interauricular intervals amounts to 0.02 sec. In line with the idea that this is a parasystolic rhythm is the fact that the longest (P)-(P) interval was shorter than the usual P-P interval, indicating that the sinus node was kept discharged by the parasystolic rhythm and only took hold when the exit block increased to a degree permitting the sinus node to escape.

When the (P)-(P) intervals, during which some sinus P-waves occur, were measured [(P)-P-(P)] (Table V), it was found that they too could be

resolved into multiples of a cycle length of  $0.16 \text{ sec.} \pm 0.01 \text{ sec.}$ , indicating again a constantly active pacemaker going at the rate of 375 per minute. This indicates the presence of entrance or protection block around the parasystolic pacemaker, preventing the sinus impulse from discharging the ectopic one, and the usual form of interference which prevents the ectopic pacemaker from acting on the heart for anywhere from 11 to 31 of its cycles.

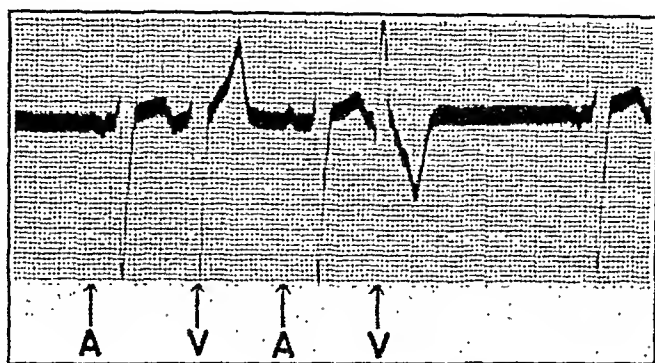


Fig. 6.

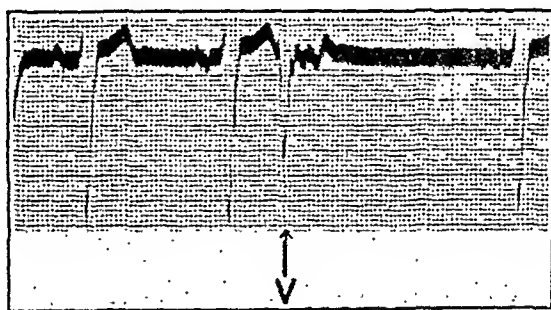


Fig. 7.

Figs. 6 and 7.—Portions of Lead III taken on Oct. 26, 1936, to show two auricular and three ventricular ectopic pacemakers identified as in Fig. 3. Discussed in text.

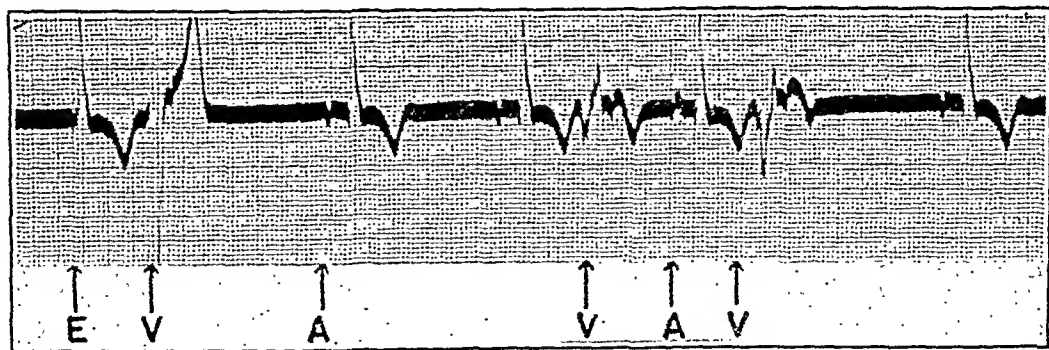


Fig. 8.—Portion of Lead IV taken on Oct. 26, 1936, to show two out of three auricular and three ventricular ectopic pacemakers identified as in Fig. 3. *E* indicates a nodal escape. Discussed in text.

The shortest interval between two P-waves in this record occurred in Lead II between  $P_3$  and  $(P)_4$ . This interval of 0.46 sec. represents the shortest duration of the refractory phase following a sinus beat and is equal to slightly less than three parasystolic cycles. The exit block was longer than this while this record was taken; the least degree was such as to block three out of four impulses of the parasystolic rhythm, but

sometimes it was such as to drop seven out of eight impulses. The paroxysmal auricular flutter in this case occurred when the exit block disappeared (or at least had a refractory phase shorter than 0.16 sec., the cycle length of the parasystolic rhythm). It is obvious that in such

TABLE V  
(P)-P-(P) INTERVALS (FIG. 1)

| LEAD I          |                  |  | LEAD II         |                  |  |
|-----------------|------------------|--|-----------------|------------------|--|
| INTERVAL        | DURATION IN SEC. | RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM | INTERVAL        | DURATION IN SEC. | RATIO OF CONDUCTED BEATS AND CYCLE LENGTH OF PARASYSTOLIC RHYTHM |
| $P_8-P_{11}$    | 3.88             | $22 \times 0.16$   | $P_2-P_4$       | 1.78             | $11 \times 0.16$   |
| $P_{14}-P_{17}$ | 3.52             | $24 \times 0.16$   | $P_4-P_6$       | 2.30             | $14 \times 0.16$   |
|                 |                  |  | $P_7-P_{11}$    | 4.56             | $28 \times 0.16$   |
| LEAD III        |                  |  | LEAD IV         |                  |  |
| $P_1-P_3$       | 1.76             | $11 \times 0.16$   | $P_1-P_2$       | 2.44             | $15 \times 0.16$   |
| $P_5-P_8$       | 3.12             | $19 \times 0.16$   | $P_6-P_8$       | 2.08             | $13 \times 0.16$   |
| $P_8-P_{10}$    | 2.16             | $14 \times 0.16$   | $P_8-P_{12}$    | 4.96             | $31 \times 0.16$   |
| $P_{10}-P_{12}$ | 2.44             | $15 \times 0.16$   | $P_{12}-P_{15}$ | 3.32             | $21 \times 0.16$   |
| $P_{12}-P_{14}$ | 2.04             | $13 \times 0.16$   |                 |                  |  |
| $P_{14}-P_{16}$ | 1.80             | $11 \times 0.16$   |                 |                  |  |
| $P_{16}-P_{18}$ | 2.08             | $13 \times 0.16$   |                 |                  |  |

0.16 = 375 beats per minute.

cases circus movement need not be invoked to explain the flutter, since a single focus mechanism as formulated by the Viennese school could adequately account for the flutter mechanism.

Figure 9 is a diagrammatic representation of our interpretation of the arrhythmia occurring in this patient when Fig. 1 was taken. *E* above shows the parasystolic rhythm with the exit block indicated by the middle horizontal line; the beats that come through are shown by the downward directed arrows. The sinus beats are shown by the upward directed arrows, and the lower horizontal line indicates the entrance block protecting the parasystolic rhythm. The interference for possession of the heart between the sinus and parasystolic rhythms can readily be worked out from this diagram.

2. *Electrocardiogram Taken Oct. 26, 1936.*—The conditions existing when this record was taken were more complex than five months earlier. Several auricular and ventricular pacemakers were found to exist at this time among the 424 beats measured and analyzed. In Lead I we were able to identify two auricular (*A*) and four ventricular (*V*) pacemakers (Fig. 3); in Lead II, three auricular and four ventricular pacemakers as well as a nodal escape (*E*) (Figs. 4 and 5); in Lead III, two auricular and three ventricular pacemakers (Figs. 6 and 7); in Lead IV, three auricular and three ventricular pacemakers, as well as a nodal escape (Fig. 8 shows only two of the three auricular pacemakers). The records also show the presence of intraventricular block of the common bundle-branch type.

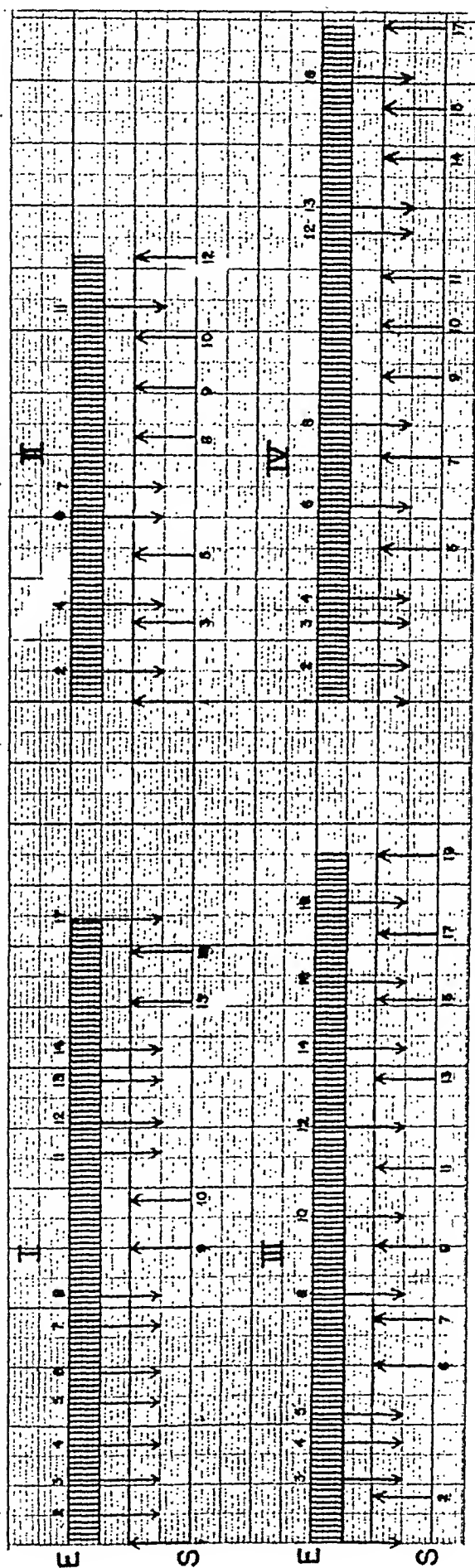


Fig. 9.—Diagram of mechanism of Fig. 1. Discussed in text.

TABLE VI

P-P INTERVALS OF FIRST FOCUS OF PARASYSTOLE (FIGS. 3-8)

| LEAD | INTERVAL                        | DURA-<br>TION<br>IN<br>SEC. | RATIO OF CON-<br>DUCTED BEATS AND<br>CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM | LEAD | INTERVAL                        | DURA-<br>TION<br>IN<br>SEC. | RATIO OF CON-<br>DUCTED BEATS AND<br>CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM |
|------|---------------------------------|-----------------------------|--|------|---------------------------------|-----------------------------|--|
| I.   | P <sub>1</sub> -P <sub>2</sub>  | 2.08                        | 10 × 0.21  |      | P <sub>2</sub> -P <sub>3</sub>  | 7.40                        | 37 × 0.20  |
|      | P <sub>1</sub> -P <sub>3</sub>  | 2.36                        | 12 × 0.20  |      | P <sub>2</sub> -P <sub>4</sub>  | 1.05                        | 5 × 0.21   |
|      | P <sub>1</sub> -P <sub>4</sub>  | 1.08                        | 5 × 0.22   |      | P <sub>2</sub> -P <sub>5</sub>  | 2.04                        | 10 × 0.20  |
|      | P <sub>1</sub> -P <sub>5</sub>  | 3.64                        | 18 × 0.20  |      | P <sub>2</sub> -P <sub>6</sub>  | 1.40                        | 7 × 0.20   |
|      | P <sub>1</sub> -P <sub>7</sub>  | 3.80                        | 19 × 0.20  |      | P <sub>2</sub> -P <sub>8</sub>  | 5.08                        | 25 × 0.20  |
|      | P <sub>1</sub> -P <sub>11</sub> | 2.44                        | 12 × 0.20  |      | P <sub>2</sub> -P <sub>11</sub> | 1.12                        | 5 × 0.22   |
|      | P <sub>1</sub> -P <sub>12</sub> | 1.40                        | 7 × 0.20   |      | P <sub>2</sub> -P <sub>12</sub> | 9.56                        | 48 × 0.20  |
|      | P <sub>1</sub> -P <sub>13</sub> | 3.80                        | 19 × 0.20  |      | P <sub>2</sub> -P <sub>13</sub> | 3.52                        | 17 × 0.21  |
|      | P <sub>1</sub> -P <sub>15</sub> | 1.00                        | 5 × 0.20   |      | P <sub>2</sub> -P <sub>15</sub> | 10.56                       | 50 × 0.21  |
|      | P <sub>1</sub> -P <sub>16</sub> | 3.56                        | 17 × 0.21  |      | P <sub>2</sub> -P <sub>16</sub> | 3.32                        | 16 × 0.21  |
|      | P <sub>1</sub> -P <sub>17</sub> | 1.24                        | 6 × 0.21   |      | P <sub>2</sub> -P <sub>17</sub> | 10.92                       | 54 × 0.20  |
|      | P <sub>1</sub> -P <sub>18</sub> | 1.16                        | 6 × 0.20   |      | P <sub>2</sub> -P <sub>18</sub> | 3.76                        | 18 × 0.21  |
|      | P <sub>1</sub> -P <sub>19</sub> | 3.88                        | 19 × 0.20  |      | P <sub>2</sub> -P <sub>19</sub> | 1.36                        | 6 × 0.23   |
|      | P <sub>1</sub> -P <sub>20</sub> | 3.76                        | 19 × 0.20  |      | P <sub>2</sub> -P <sub>20</sub> | 2.48                        | 12 × 0.21  |
|      | P <sub>1</sub> -P <sub>21</sub> | 1.40                        | 7 × 0.20   |      | P <sub>2</sub> -P <sub>21</sub> | 1.24                        | 6 × 0.21   |
|      | P <sub>1</sub> -P <sub>22</sub> | 3.84                        | 19 × 0.20  |      | P <sub>2</sub> -P <sub>22</sub> | 1.24                        | 6 × 0.21   |
|      | P <sub>1</sub> -P <sub>23</sub> | 1.48                        | 7 × 0.21   |      | P <sub>2</sub> -P <sub>23</sub> | 4.68                        | 23 × 0.20  |
|      | P <sub>1</sub> -P <sub>24</sub> | 2.24                        | 11 × 0.20  |      | P <sub>2</sub> -P <sub>24</sub> | 1.44                        | 7 × 0.21   |
|      | P <sub>1</sub> -P <sub>25</sub> | 3.96                        | 20 × 0.20  |      | P <sub>2</sub> -P <sub>25</sub> | 2.20                        | 11 × 0.20  |
|      | P <sub>1</sub> -P <sub>26</sub> | 1.44                        | 7 × 0.21   |      | P <sub>2</sub> -P <sub>26</sub> | 1.28                        | 6 × 0.21   |
|      | P <sub>1</sub> -P <sub>27</sub> | 3.84                        | 19 × 0.20  |      |                                 |                             |  |
|      | P <sub>1</sub> -P <sub>28</sub> | 1.24                        | 6 × 0.21   | III. | P <sub>3</sub> -P <sub>4</sub>  | 2.56                        | 12 × 0.21  |
|      | P <sub>1</sub> -P <sub>29</sub> | 1.28                        | 6 × 0.21   |      | P <sub>3</sub> -P <sub>5</sub>  | 1.40                        | 7 × 0.20   |
|      | P <sub>1</sub> -P <sub>30</sub> | 1.04                        | 5 × 0.21   |      | P <sub>3</sub> -P <sub>6</sub>  | 3.16                        | 16 × 0.20  |
|      | P <sub>1</sub> -P <sub>31</sub> | 0.56                        | 3 × 0.20   |      | P <sub>3</sub> -P <sub>7</sub>  | 2.92                        | 14 × 0.21  |
|      | P <sub>1</sub> -P <sub>32</sub> | 2.96                        | 15 × 0.20  |      | P <sub>3</sub> -P <sub>8</sub>  | 6.24                        | 31 × 0.20  |
|      | P <sub>1</sub> -P <sub>33</sub> | 1.12                        | 5 × 0.22   |      | P <sub>3</sub> -P <sub>9</sub>  | 1.32                        | 6 × 0.22   |
|      | P <sub>1</sub> -P <sub>34</sub> | 4.84                        | 24 × 0.20  |      | P <sub>3</sub> -P <sub>10</sub> | 2.44                        | 12 × 0.20  |
|      | P <sub>1</sub> -P <sub>35</sub> | 5.16                        | 26 × 0.20  |      | P <sub>3</sub> -P <sub>11</sub> | 1.44                        | 7 × 0.21   |
|      | P <sub>1</sub> -P <sub>36</sub> | 4.16                        | 21 × 0.20  |      | P <sub>3</sub> -P <sub>12</sub> | 8.28                        | 41 × 0.20  |
|      | P <sub>1</sub> -P <sub>37</sub> | 3.92                        | 19 × 0.21  |      | P <sub>3</sub> -P <sub>13</sub> | 1.32                        | 6 × 0.22   |
|      | P <sub>1</sub> -P <sub>38</sub> | 3.56                        | 17 × 0.21  |      | P <sub>3</sub> -P <sub>14</sub> | 1.08                        | 5 × 0.22   |
|      | P <sub>1</sub> -P <sub>39</sub> | 1.08                        | 5 × 0.22   |      | P <sub>3</sub> -P <sub>15</sub> | 6.40                        | 32 × 0.20  |
|      | P <sub>1</sub> -P <sub>40</sub> | 5.04                        | 25 × 0.20  |      | P <sub>3</sub> -P <sub>16</sub> | 1.24                        | 6 × 0.21   |
|      | P <sub>1</sub> -P <sub>41</sub> | 1.04                        | 5 × 0.21   |      | P <sub>3</sub> -P <sub>17</sub> | 1.08                        | 5 × 0.22   |
|      | P <sub>1</sub> -P <sub>42</sub> | 5.36                        | 26 × 0.21  |      | P <sub>3</sub> -P <sub>18</sub> | 3.92                        | 19 × 0.21  |
|      | P <sub>1</sub> -P <sub>43</sub> | 3.72                        | 18 × 0.21  |      | P <sub>3</sub> -P <sub>19</sub> | 3.84                        | 19 × 0.20  |
|      | P <sub>1</sub> -P <sub>44</sub> | 1.12                        | 5 × 0.22   |      | P <sub>3</sub> -P <sub>20</sub> | 1.48                        | 7 × 0.21   |
|      | P <sub>1</sub> -P <sub>45</sub> | 3.92                        | 19 × 0.21  |      | P <sub>3</sub> -P <sub>21</sub> | 2.32                        | 11 × 0.21  |
|      | P <sub>1</sub> -P <sub>46</sub> | 1.20                        | 6 × 0.20   |      | P <sub>3</sub> -P <sub>22</sub> | 2.36                        | 11 × 0.21  |
|      | P <sub>1</sub> -P <sub>47</sub> | 8.72                        | 42 × 0.21  |      | P <sub>3</sub> -P <sub>23</sub> | 1.36                        | 6 × 0.23   |
|      | P <sub>1</sub> -P <sub>48</sub> | 2.40                        | 12 × 0.20  |      | P <sub>3</sub> -P <sub>24</sub> | 3.76                        | 18 × 0.21  |
|      | P <sub>1</sub> -P <sub>49</sub> | 1.20                        | 6 × 0.20   |      | P <sub>3</sub> -P <sub>25</sub> | 1.44                        | 7 × 0.21   |
| II.  | P <sub>3</sub> -P <sub>4</sub>  | 1.36                        | 6 × 0.23   |      | P <sub>3</sub> -P <sub>26</sub> | 2.40                        | 12 × 0.20  |
|      | P <sub>3</sub> -P <sub>5</sub>  | 2.80                        | 14 × 0.20  |      | P <sub>3</sub> -P <sub>27</sub> | 1.44                        | 7 × 0.21   |
|      | P <sub>3</sub> -P <sub>6</sub>  | 4.04                        | 20 × 0.20  |      | P <sub>3</sub> -P <sub>28</sub> | 3.88                        | 19 × 0.20  |
|      | P <sub>3</sub> -P <sub>11</sub> | 1.32                        | 6 × 0.22   |      | P <sub>3</sub> -P <sub>29</sub> | 4.20                        | 21 × 0.20  |
|      | P <sub>3</sub> -P <sub>12</sub> | 1.04                        | 5 × 0.21   |      | P <sub>3</sub> -P <sub>30</sub> | 1.48                        | 7 × 0.21   |
|      | P <sub>3</sub> -P <sub>13</sub> | 6.40                        | 32 × 0.20  |      | P <sub>3</sub> -P <sub>31</sub> | 2.72                        | 13 × 0.21  |
|      | P <sub>3</sub> -P <sub>14</sub> | 1.40                        | 7 × 0.20   |      | P <sub>3</sub> -P <sub>32</sub> | 6.20                        | 31 × 0.20  |
|      | P <sub>3</sub> -P <sub>15</sub> | 2.60                        | 13 × 0.20  |      | P <sub>3</sub> -P <sub>33</sub> | 1.48                        | 7 × 0.21   |
|      | P <sub>3</sub> -P <sub>16</sub> | 1.52                        | 8 × 0.19   |      | P <sub>3</sub> -P <sub>34</sub> | 3.76                        | 18 × 0.21  |
|      | P <sub>3</sub> -P <sub>17</sub> | 4.56                        | 23 × 0.20  |      | P <sub>3</sub> -P <sub>35</sub> | 0.88                        | 4 × 0.22   |
|      | P <sub>3</sub> -P <sub>18</sub> | 1.44                        | 7 × 0.21   |      | P <sub>3</sub> -P <sub>36</sub> | 2.28                        | 11 × 0.21  |
|      | P <sub>3</sub> -P <sub>19</sub> | 6.28                        | 31 × 0.20  |      | P <sub>3</sub> -P <sub>37</sub> | 3.92                        | 19 × 0.20  |
|      | P <sub>3</sub> -P <sub>20</sub> | 1.48                        | 7 × 0.21   |      | P <sub>3</sub> -P <sub>38</sub> | 1.24                        | 6 × 0.21   |
|      | P <sub>3</sub> -P <sub>21</sub> | 1.36                        | 6 × 0.23   |      | P <sub>3</sub> -P <sub>39</sub> | 7.84                        | 39 × 0.20  |
|      | P <sub>3</sub> -P <sub>22</sub> | 1.36                        | 6 × 0.23   |      | P <sub>3</sub> -P <sub>40</sub> | 3.76                        | 18 × 0.21  |

TABLE VI—CONT'D

| LEAD | INTERVAL                           | DURA-<br>TION<br>IN<br>SEC. | RATIO OF CON-<br>DUCTED BEATS AND<br>CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM | LEAD | INTERVAL                         | DURA-<br>TION<br>IN<br>SEC. | RATIO OF CON-<br>DUCTED BEATS AND<br>CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM |
|------|------------------------------------|-----------------------------|--|------|----------------------------------|-----------------------------|--|
|      | P <sub>102</sub> -P <sub>103</sub> | 1.28                        | 6 × 0.21   |      | P <sub>27</sub> -P <sub>28</sub> | 1.36                        | 7 × 0.20   |
|      | P <sub>103</sub> -P <sub>105</sub> | 2.24                        | 11 × 0.20  |      | P <sub>28</sub> -P <sub>29</sub> | 1.08                        | 5 × 0.22   |
|      | P <sub>105</sub> -P <sub>107</sub> | 2.32                        | 11 × 0.21  |      | P <sub>29</sub> -P <sub>31</sub> | 2.24                        | 11 × 0.20  |
|      | P <sub>107</sub> -P <sub>108</sub> | 1.40                        | 7 × 0.20   |      | P <sub>31</sub> -P <sub>32</sub> | 1.36                        | 7 × 0.20   |
|      | P <sub>108</sub> -P <sub>115</sub> | 7.20                        | 36 × 0.20  |      | P <sub>32</sub> -P <sub>34</sub> | 2.36                        | 11 × 0.21  |
|      | P <sub>115</sub> -P <sub>116</sub> | 1.20                        | 6 × 0.20   |      | P <sub>34</sub> -P <sub>35</sub> | 1.40                        | 7 × 0.20   |
|      | P <sub>116</sub> -P <sub>120</sub> | 5.12                        | 25 × 0.20  |      | P <sub>35</sub> -P <sub>40</sub> | 5.16                        | 25 × 0.21  |
|      | P <sub>120</sub> -P <sub>121</sub> | 1.24                        | 6 × 0.21   |      | P <sub>40</sub> -P <sub>41</sub> | 1.16                        | 6 × 0.20   |
|      | P <sub>121</sub> -P <sub>122</sub> | 1.24                        | 6 × 0.21   |      | P <sub>41</sub> -P <sub>44</sub> | 3.36                        | 16 × 0.21  |
|      | P <sub>122</sub> -P <sub>124</sub> | 2.32                        | 11 × 0.21  |      | P <sub>44</sub> -P <sub>46</sub> | 2.36                        | 11 × 0.21  |
|      | P <sub>124</sub> -P <sub>126</sub> | 2.20                        | 11 × 0.20  |      | P <sub>46</sub> -P <sub>50</sub> | 3.76                        | 18 × 0.21  |
|      | P <sub>126</sub> -P <sub>127</sub> | 1.36                        | 6 × 0.23   |      | P <sub>50</sub> -P <sub>51</sub> | 1.40                        | 7 × 0.20   |
|      | P <sub>127</sub> -P <sub>131</sub> | 3.88                        | 19 × 0.20  |      | P <sub>51</sub> -P <sub>52</sub> | 1.08                        | 5 × 0.22   |
|      | P <sub>131</sub> -P <sub>132</sub> | 1.20                        | 6 × 0.20   |      | P <sub>52</sub> -P <sub>54</sub> | 2.20                        | 11 × 0.20  |
| IV.  | P <sub>1</sub> -P <sub>3</sub>     | 2.40                        | 12 × 0.20  |      | P <sub>54</sub> -P <sub>55</sub> | 1.16                        | 6 × 0.20   |
|      | P <sub>3</sub> -P <sub>4</sub>     | 1.08                        | 5 × 0.22   |      | P <sub>55</sub> -P <sub>61</sub> | 5.74                        | 28 × 0.21  |
|      | P <sub>4</sub> -P <sub>6</sub>     | 2.32                        | 11 × 0.21  |      | P <sub>61</sub> -P <sub>62</sub> | 1.32                        | 6 × 0.22   |
|      | P <sub>6</sub> -P <sub>7</sub>     | 0.80                        | 4 × 0.20   |      | P <sub>62</sub> -P <sub>63</sub> | 1.44                        | 7 × 0.21   |
|      | P <sub>7</sub> -P <sub>8</sub>     | 1.28                        | 6 × 0.21   |      | P <sub>63</sub> -P <sub>64</sub> | 1.16                        | 6 × 0.20   |
|      | P <sub>8</sub> -P <sub>9</sub>     | 1.40                        | 7 × 0.20   |      | P <sub>64</sub> -P <sub>66</sub> | 2.44                        | 12 × 0.20  |
|      | P <sub>9</sub> -P <sub>13</sub>    | 3.60                        | 18 × 0.20  |      | P <sub>66</sub> -P <sub>67</sub> | 1.04                        | 5 × 0.21   |
|      | P <sub>13</sub> -P <sub>14</sub>   | 1.40                        | 7 × 0.20   |      | P <sub>67</sub> -P <sub>72</sub> | 6.29                        | 31 × 0.20  |
|      | P <sub>14</sub> -P <sub>16</sub>   | 2.48                        | 12 × 0.21  |      | P <sub>72</sub> -P <sub>73</sub> | 1.24                        | 6 × 0.21   |
|      | P <sub>16</sub> -P <sub>19</sub>   | 3.68                        | 18 × 0.21  |      | P <sub>73</sub> -P <sub>77</sub> | 4.92                        | 24 × 0.21  |
|      | P <sub>19</sub> -P <sub>20</sub>   | 1.04                        | 5 × 0.21   |      | P <sub>77</sub> -P <sub>78</sub> | 1.40                        | 7 × 0.20   |
|      | P <sub>20</sub> -P <sub>24</sub>   | 4.68                        | 23 × 0.20  |      | P <sub>78</sub> -P <sub>84</sub> | 6.88                        | 34 × 0.21  |
|      | P <sub>24</sub> -P <sub>25</sub>   | 1.36                        | 7 × 0.20   |      | P <sub>84</sub> -P <sub>85</sub> | 3.92                        | 19 × 0.21  |
|      | P <sub>25</sub> -P <sub>27</sub>   | 2.40                        | 12 × 0.20  |      | P <sub>85</sub> -P <sub>89</sub> | 0.88                        | 4 × 0.22   |

0.19 = 316 beats per minute.

0.20 = 300 beats per minute.

0.21 = 286 beats per minute.

0.22 = 272 beats per minute.

0.23 = 261 beats per minute.

All the P-P intervals of the various auricular and all the R-R intervals of the various ventricular pacemakers were measured. While it was easy to find common divisors for both the auricular and ventricular pacemakers in each lead, it was not possible to match the ventricular pacemakers of one lead with those of the others with any degree of certainty. We, therefore, can only surmise that a number of parasystolic foci were operating in the ventricles, interfering with one another (and with the impulses coming to the ventricle via the A-V junctional tissue) for possession of the ventricles. There was no conclusive evidence of exit block in these ventricular foci, the cycle length of the parasystolic rhythms being sufficiently long so that interference of the various foci could explain all the findings.

In the case of the auricular parasystolic rhythms, the 242 cycle measured in the various leads could be divided into three types, each with its own common divisor (Tables VI, VII and VIII). No evidence of a sinus rhythm could be made out; apparently the auricles were entirely under the control of these three parasystolic rhythms competing with



each other. While interference alone might have explained the occurrence of the heartbeats arising from one of these foci, exit block has to be invoked in the other two, if our calculations of the cycle length of the parasystolic rhythms are correct.

3. *Electrocardiogram Taken July 7, 1932.*—It is interesting that the record taken four and one-half years before (Fig. 2) also showed three auricular pacemakers which on analysis show common divisors approximately equal to those found on Oct. 26, 1936 (Table IX). This would indicate that these parasystolic rhythms had been present for at least four and one-half years. Ventricular extrasystoles were also present at this time but were not as frequent or from as many foci as in the long record referred to above.

TABLE VII  
P-P INTERVALS OF SECOND FOCUS OF PARASYSTOLE (FIGS. 3-8)

| LEAD | INTERVAL                         | DURATION<br>IN<br>SEC. | RATIO OF CON-<br>DUCTED BEATS AND<br>CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM | LEAD | INTERVAL                           | DURATION<br>IN<br>SEC. | RATIO OF CON-<br>DUCTED BEATS AND<br>CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM |
|------|----------------------------------|------------------------|--|------|------------------------------------|------------------------|--|
| II.  | P <sub>12</sub> -P <sub>15</sub> | 10.72                  | 26 × 0.41  |      | P <sub>12</sub> -P <sub>15</sub>   | 6.48                   | 16 × 0.41  |
|      | P <sub>15</sub> -P <sub>18</sub> | 11.60                  | 29 × 0.40  |      | P <sub>15</sub> -P <sub>18</sub>   | 1.44                   | 4 × 0.36   |
|      | P <sub>18</sub> -P <sub>21</sub> | 4.64                   | 11 × 0.42  |      | P <sub>18</sub> -P <sub>21</sub>   | 2.52                   | 6 × 0.42   |
|      | P <sub>21</sub> -P <sub>24</sub> | 1.24                   | 3 × 0.41   |      | P <sub>21</sub> -P <sub>24</sub>   | 3.68                   | 9 × 0.41   |
| III. | P <sub>1</sub> -P <sub>4</sub>   | 2.16                   | 5 × 0.43   |      | P <sub>101</sub> -P <sub>104</sub> | 9.96                   | 25 × 0.40  |
|      | P <sub>4</sub> -P <sub>7</sub>   | 3.84                   | 9 × 0.43   |      | P <sub>104</sub> -P <sub>107</sub> | 2.88                   | 7 × 0.41   |
|      | P <sub>7</sub> -P <sub>10</sub>  | 1.48                   | 4 × 0.37   |      | P <sub>107</sub> -P <sub>110</sub> | 1.64                   | 4 × 0.41   |
|      | P <sub>10</sub> -P <sub>13</sub> | 9.16                   | 22 × 0.42  |      | P <sub>110</sub> -P <sub>113</sub> | 4.92                   | 12 × 0.41  |
|      | P <sub>13</sub> -P <sub>16</sub> | 2.52                   | 6 × 0.42   |      | P <sub>113</sub> -P <sub>116</sub> | 12.44                  | 31 × 0.40  |
|      | P <sub>16</sub> -P <sub>19</sub> | 2.64                   | 7 × 0.38   | IV.  | P <sub>11</sub> -P <sub>14</sub>   | 8.56                   | 21 × 0.41  |
|      | P <sub>19</sub> -P <sub>22</sub> | 6.28                   | 15 × 0.42  |      | P <sub>14</sub> -P <sub>17</sub>   | 4.56                   | 11 × 0.42  |
|      | P <sub>22</sub> -P <sub>25</sub> | 1.56                   | 4 × 0.39   |      | P <sub>17</sub> -P <sub>20</sub>   | 17.40                  | 43 × 0.40  |
|      | P <sub>25</sub> -P <sub>28</sub> | 7.12                   | 18 × 0.40  |      | P <sub>20</sub> -P <sub>23</sub>   | 1.48                   | 4 × 0.37   |
|      | P <sub>28</sub> -P <sub>31</sub> | 3.12                   | 8 × 0.39   |      | P <sub>23</sub> -P <sub>26</sub>   | 4.76                   | 12 × 0.40  |
|      | P <sub>31</sub> -P <sub>34</sub> | 11.32                  | 29 × 0.39  |      | P <sub>26</sub> -P <sub>29</sub>   | 4.84                   | 12 × 0.40  |
|      | P <sub>34</sub> -P <sub>37</sub> | 10.00                  | 25 × 0.40  |      | P <sub>29</sub> -P <sub>32</sub>   | 12.04                  | 30 × 0.40  |
|      | P <sub>37</sub> -P <sub>40</sub> | 2.96                   | 7 × 0.42   |      | P <sub>32</sub> -P <sub>35</sub>   | 12.01                  | 30 × 0.40  |
|      | P <sub>40</sub> -P <sub>43</sub> | 5.64                   | 14 × 0.40  |      | P <sub>35</sub> -P <sub>38</sub>   | 2.56                   | 6 × 0.43   |
|      | P <sub>43</sub> -P <sub>46</sub> | 3.60                   | 9 × 0.40   |      | P <sub>38</sub> -P <sub>41</sub>   | 4.96                   | 12 × 0.41  |
|      | P <sub>46</sub> -P <sub>49</sub> | 1.52                   | 4 × 0.38   |      | P <sub>41</sub> -P <sub>44</sub>   | 5.36                   | 13 × 0.41  |
|      | P <sub>49</sub> -P <sub>52</sub> | 5.16                   | 13 × 0.39  |      | P <sub>44</sub> -P <sub>47</sub>   | 2.36                   | 6 × 0.39   |
|      | P <sub>52</sub> -P <sub>55</sub> | 4.80                   | 12 × 0.40  |      | P <sub>47</sub> -P <sub>50</sub>   | 1.56                   | 4 × 0.39   |
|      | P <sub>55</sub> -P <sub>58</sub> | 7.16                   | 18 × 0.40  |      | P <sub>50</sub> -P <sub>53</sub>   | 3.00                   | 7 × 0.43   |

0.37 = 162 beats per minute.  
 0.38 = 158 beats per minute.  
 0.39 = 154 beats per minute.  
 0.40 = 150 beats per minute.  
 0.41 = 146 beats per minute.  
 0.42 = 142 beats per minute.  
 0.43 = 140 beats per minute.

#### SUMMARY

A case is reported of arteriosclerotic heart disease with sinus bradycardia and intraventricular block which on one occasion showed an electrocardiogram with an auricular parasystole competing with the sinus rhythm. Evidence is given that the parasystolic focus was beating at

TABLE VIII

P-P INTERVALS OF THIRD FOCUS OF PARASYSTOLE (FIGS. 3-8)

| LEAD | INTERVAL                           | DURA-<br>TION<br>IN<br>SEC. | RATIO OF CON-<br>DUCTED BEATS AND<br>CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM | LEAD | INTERVAL                         | DURA-<br>TION<br>IN<br>SEC. | RATIO OF CON-<br>DUCTED BEATS AND<br>CYCLE LENGTH OF<br>PARASYSTOLIC<br>RHYTHM |
|------|------------------------------------|-----------------------------|--|------|----------------------------------|-----------------------------|--|
| I.   | P <sub>11</sub> -P <sub>17</sub>   | 6.60                        | 9 × 0.73   | II.  | P <sub>1</sub> -P <sub>6</sub>   | 5.16                        | 7 × 0.74   |
|      | P <sub>17</sub> -P <sub>22</sub>   | 5.36                        | 7 × 0.77   |      | P <sub>6</sub> -P <sub>9</sub>   | 3.80                        | 5 × 0.76   |
|      | P <sub>22</sub> -P <sub>27</sub>   | 6.36                        | 8 × 0.80   |      | P <sub>9</sub> -P <sub>14</sub>  | 6.36                        | 8 × 0.80   |
|      | P <sub>27</sub> -P <sub>30</sub>   | 2.92                        | 4 × 0.73   |      | P <sub>14</sub> -P <sub>16</sub> | 1.52                        | 2 × 0.76   |
|      | P <sub>30</sub> -P <sub>35</sub>   | 5.24                        | 7 × 0.75   |      | P <sub>16</sub> -P <sub>24</sub> | 10.36                       | 14 × 0.74  |
|      | P <sub>35</sub> -P <sub>47</sub>   | 12.92                       | 17 × 0.76  |      | P <sub>24</sub> -P <sub>29</sub> | 6.04                        | 8 × 0.76   |
|      | P <sub>47</sub> -P <sub>55</sub>   | 7.80                        | 10 × 0.78  |      | P <sub>29</sub> -P <sub>31</sub> | 1.56                        | 2 × 0.78   |
|      | P <sub>55</sub> -P <sub>59</sub>   | 5.12                        | 7 × 0.73   |      | P <sub>31</sub> -P <sub>33</sub> | 8.80                        | 12 × 0.73  |
|      | P <sub>59</sub> -P <sub>67</sub>   | 9.12                        | 12 × 0.76  |      | P <sub>33</sub> -P <sub>40</sub> | 1.48                        | 2 × 0.74   |
|      | P <sub>67</sub> -P <sub>68</sub>   | 1.56                        | 2 × 0.78   |      | P <sub>40</sub> -P <sub>45</sub> | 8.24                        | 11 × 0.75  |
|      | P <sub>68</sub> -P <sub>71</sub>   | 3.56                        | 5 × 0.71   |      | P <sub>45</sub> -P <sub>62</sub> | 23.68                       | 32 × 0.74  |
|      | P <sub>71</sub> -P <sub>76</sub>   | 3.06                        | 4 × 0.74   |      | P <sub>62</sub> -P <sub>72</sub> | 12.60                       | 17 × 0.74  |
|      | P <sub>76</sub> -P <sub>81</sub>   | 5.52                        | 7 × 0.79   |      | P <sub>72</sub> -P <sub>79</sub> | 7.72                        | 10 × 0.77  |
|      | P <sub>81</sub> -P <sub>86</sub>   | 6.08                        | 8 × 0.76   |      | P <sub>79</sub> -P <sub>85</sub> | 11.04                       | 15 × 0.74  |
|      | P <sub>86</sub> -P <sub>87</sub>   | 1.56                        | 2 × 0.78   | IV.  | P <sub>2</sub> -P <sub>10</sub>  | 9.24                        | 12 × 0.77  |
|      | P <sub>87</sub> -P <sub>94</sub>   | 8.76                        | 12 × 0.73  |      | P <sub>10</sub> -P <sub>15</sub> | 5.08                        | 7 × 0.73   |
|      | P <sub>94</sub> -P <sub>95</sub>   | 4.12                        | 5 × 0.82   |      | P <sub>15</sub> -P <sub>25</sub> | 13.28                       | 17 × 0.78  |
|      | P <sub>95</sub> -P <sub>100</sub>  | 2.40                        | 3 × 0.80   |      | P <sub>25</sub> -P <sub>35</sub> | 67.97                       | 90 × 0.76  |
|      | P <sub>100</sub> -P <sub>102</sub> | 1.56                        | 2 × 0.78   |      | P <sub>35</sub> -P <sub>57</sub> | 1.56                        | 2 × 0.78   |
|      | P <sub>102</sub> -P <sub>104</sub> | 2.44                        | 3 × 0.81   |      |                                  |                             |  |

0.71 = 85 beats per minute.  
 0.73 = 82 beats per minute.  
 0.74 = 81 beats per minute.  
 0.75 = 80 beats per minute.  
 0.76 = 79 beats per minute.  
 0.77 = 78 beats per minute.

0.78 = 77 beats per minute.  
 0.79 = 76 beats per minute.  
 0.80 = 75 beats per minute.  
 0.81 = 74 beats per minute.  
 0.82 = 73 beats per minute.

the rate of 375 per minute and had exit block (as postulated by Kaufmann and Rothberger). This is apparently the first case with definite evidence of exit block on record.

An electrocardiogram taken subsequently showed sinus rhythm absent and gave evidence of multiple auricular and ventricular foci of impulse initiation. Three auricular and at least four ventricular foci were identified as well as an occasional nodal escape. The parasystolic character of the ventricular rhythms was suggested by the evidence but could not be established with certainty since the cycles in each lead were too few and the beats in one lead could not be accurately identified with beats in other leads. The three auricular rhythms could be shown on the basis of measurements of 242 cycles to be parasystolic in origin with exit block present in at least two of them.

A record taken about four and one-half years before showed the same three auricular parasystolic rhythms occurring at approximately the same rate. This demonstrates the long persistence of parasystolic pace-makers.

The attacks of rapid heart action in this patient, which resembled paroxysmal tachycardia and auricular flutter, seem to be correlated with lessening of the exit block at least in the case of the auricular rhythms.



This case we believe lends support to the parasystolic theory expounded by Rothberger and his colleagues and seems to give clear proof of the existence of exit block.

## REFERENCES

1. Wenckebach, K. F., and Winterberg, H.: *Unregelmässige Herztätigkeit*, Leipzig, 1927, W. Engelmann.
2. Lewis, T.: *The Mechanism and Graphic Registration of the Heart Beat*, ed. 3, London, 1925, Shaw and Sons.
3. Rothberger, C. J.: Normale und pathologische Physiologie der Rhythmik und Koordination des Herzens, *Ergebn. d. Physiol.* 32: 427, 1931.
4. Kaufmann, R., and Rothberger, C. J.: *Ztschr. f. d. ges. exper. Med.* 7: 199, 1919.
5. Singer, R., and Winterberg, H.: *Wien. Arch. f. inn. Med.* 1: 391, 1920.
6. Scherf, D.: *Ztschr. f. d. ges. exper. Med.* 51: 816, 1926.
7. Faltischek, F., and Scherf, D.: *Wien. Arch. f. inn. Med.* 23: 269, 1932.
8. Jervell, A.: *Acta med. Scandinav.* 79: 239, 1932.
9. Hill, J. G. W., and Cameron, J. D. S.: *AM. HEART J.* 11: 140, 1936.

# THE ELECTRICAL AXIS IN SIMULTANEOUS LEADS

## I. FACTORS INCREASING THE DISPERSION OF NORMAL VALUES\*

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### INTRODUCTION

A CONSPICUOUS feature of the electrocardiogram that both invites computation and resists analysis is the difference in amplitude of its component waves. This problem presents two phases, the origin of the primary distinction between individual portions of a single cycle, and the source of the secondary modifications to which each wave is susceptible. Since the most sensitive index for the description of these waves is found in the electrical axis, for the measurement of which suitable apparatus has not been generally available, further study is in order.

As recognized by Einthoven and his coworkers<sup>1</sup> (1913), the shape of an electrocardiogram is conditioned by the position of the electrodes in relation to the heart. This is in accord with the proposition that the passage of an electrical current in a given circuit will exert a maximum effect upon electrodes in a secondary circuit if that is parallel to the first, and the current will have no effect upon a secondary circuit placed at right-angles to itself (Millikan and Mills, p. 15<sup>2</sup>). Conversely, if the orientation of the primary circuit were unknown it could be discovered by moving the secondary electrodes about it until the maximum effect was obtained: then the axis connecting these electrodes will be parallel to the primary or electrical axis (Trendelenburg, 1932-33<sup>3</sup>). In the case of the heart the direction of the flow of the electrical impulse may be similarly discovered but it is not necessary to rotate the electrodes because, by using Einthoven's triangular arrangement of the electrodes it is possible to calculate the electrical axis from the three standard leads. This principle accounts for the altered appearance of a given wave in different leads.

It is also known (Kahn 1909,<sup>4</sup> Fahr 1912,<sup>5</sup> Williams 1914,<sup>6</sup> Lewis 1925, chapter 8, p. 123, 127;<sup>7</sup> Meek and Wilson 1925<sup>8</sup>) that the electrical axis of the heart is not constant throughout the cycle, varying from instant to instant as though the spread of the excitation wave followed a changing (i. e., nonrectilinear) course. Assuming that the Purkinje system constitutes the excitation pathway it is obvious that certain regions will lie parallel to one of the three standard leads (Robb, Greene and Robb, 1937<sup>9</sup>). Hence, these regions will be fully represented in the corresponding lead. On the other hand, all those pathways not

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in the frontal plane will be less adequately recorded, and those portions of the Purkinje system that lie at right angles to the frontal plane will have little, if any, effect on any standard lead. The former regions probably correspond to the "favored regions" of Katz and his associates<sup>10</sup> and the latter portions would constitute the "silent areas" of coronary thrombosis. These conclusions offer a theoretical justification for the use of chest leads; furthermore, the changing direction of the excitation wave during each cycle offers a physical basis on which to explain the differences of amplitude and duration characteristic of the several component waves of an electrocardiogram.

#### SOURCES OF ERROR

It is obvious that the progress of excitation in the heart is a three dimensional phenomenon which is also a function of time. If the electrical axis be defined as the apparent direction of the excitation wave, one must concede that its satisfactory description requires four dimensions. Most of the published observations include only the two dimensions of the frontal plane, intercepted at an arbitrary point in time which is assumed to be comparable in clinical tracings. It is not surprising that tremendous normal variations are accepted. Thus, applying Einthoven's equation to the R-waves alone,

|  |                          |
|--|--------------------------|
| Einthoven, Fahr, and De Waart <sup>1</sup>                       | give as normal 40 to 90° |
| Waller <sup>11</sup>   | -10 to 100°              |
| Carter, Richter, and Green, <sup>12</sup> Dieuaide <sup>23</sup> | 0 to 90°                 |
| Lewis <sup>7</sup>   | 75 (about)               |
| Pardee <sup>13</sup>   | 30 to 90°                |
| Proger and Davis <sup>14</sup>                                   | 0 to 80°                 |
| White <sup>15</sup>  | 0 to 90°                 |

Even if it be assumed that the axis of the R-wave is peculiarly sensitive to abnormal conditions outside the bundle of His, its evaluation presents major difficulties, each of which contributes to the dispersion of normal values.

1. *Phase Error*.—It is often impossible to identify synchronous points in the several leads unless they were recorded simultaneously. Thus White (1937, p. 130) mentions that the leads are frequently "out of phase." This is evidenced by lack of conformity to the equation:  $E^2 = E^1 + E^3$  (Wilson, McLeod, Barker, 1931-32<sup>16</sup>). Williams (1914<sup>6</sup>) reports 5 cases in 6 out of phase. We have noted this discrepancy in about 60 per cent of the electrocardiograms published by Carter (1937<sup>17</sup>) and in 80 per cent of those given by Pardee (1933<sup>18</sup>). In all of these records no legitimate calculation of the "R-axis" is possible, because, as shown in Fig. 1, there is no one R-axis to measure. If, as in a recent patient, the three R-waves, 1, 2, and 3 are 3, 6 and 6 mm. respectively, who can say which one (or two) values are misleading? Regarding

this contingency Jones and Roberts (1929<sup>16</sup>) remark "rarely do perpendiculars of all three leads fall on one point; it is simpler to use only Leads I and II." Herrmann and Wilson<sup>20</sup> suggest the use of the two largest, and Proger and Davis (1930<sup>14</sup>) prefer Leads I and II in cases of left ventricular preponderance and II and III in right ventricular preponderance as previously suggested by Pardee (1920<sup>13</sup>). Unless simultaneous points are recognizable there exists no legitimate method for calculating any axis in out-of-phase records.

2. *Inconsistency in Calculation.*—It is not permissible to include in a single class for comparison electrical axes calculated by different methods, because R may have a different value in each lead, as shown in Table I.

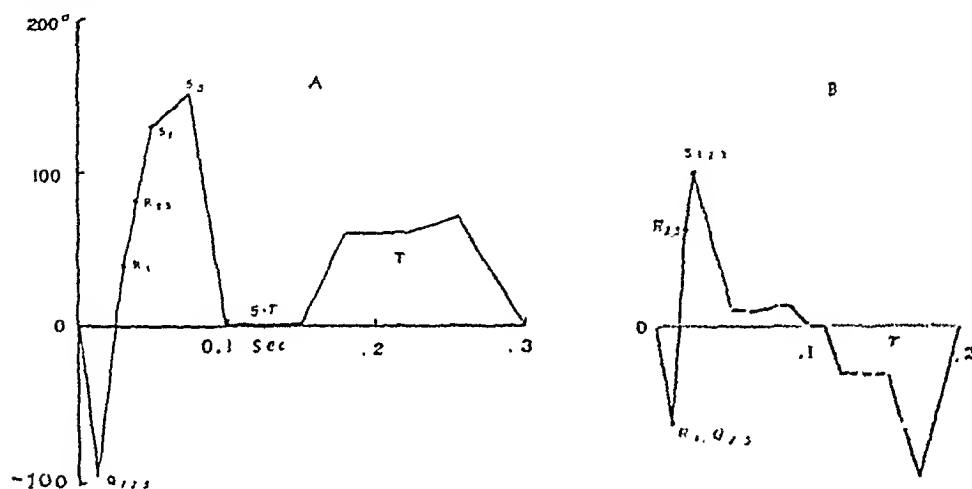


Fig. 1.—Electrical axes plotted at 2 to 10 sigma intervals throughout the (ventricular) cycle; A: man, B: a dog with negative T.

Note that the  $R_1$  and  $R_2$ -peaks of the standard leads were not synchronous, and have axes differing 50 and 100°, respectively.

In five of these six records the axis of  $R_2$  differs from that of  $R_1$  by about one hundred degrees. These details are obscured when some hybrid estimate is attempted, as is the current usage; such estimates have no real existence and very little empirical value. Thus Carter's<sup>17</sup>

TABLE I  
DISCREPANCIES BETWEEN METHODS OF CALCULATING ELECTRICAL AXES  
IN OUT-OF-PHASE RECORDS

| Patient | R-PEAKS, AS IN<br>CONSECUTIVE RECORDS |                | HOMOLOGOUS POINTS, AS IN<br>SIMULTANEOUS RECORDS |       |       |
|---------|---------------------------------------|----------------|--|-------|-------|
|         | $R^1 + R^2$                           | $R^2 \div R^3$ | $R^1$  | $R^2$ | $R^3$ |
| A       | 0*                                    | 33             | 4  | 12    | -90   |
| B       | 6*                                    | 44             | -42  | 48    | 70    |
| C       | 20*                                   | 40             | 17   | 40    | 120   |
| D       | 20*                                   | 44             | 16   | 16    | 150   |
| E       | 30*                                   | 56             | 30   | 48    | 120   |
| F       | 84                                    | 94*            | 60   | 93    | 104   |

\*Asterisk denotes angle derived by calculation from the two largest peaks; numbers represent degrees from the horizontal, advancing clockwise from the left side.

prime examples of right axis deviation, given in his Fig. 18, in order of severity, calculated from Leads I and II are: 65, 74, 81, 83, and 85°; recalculated from II and III, these are: 86, 85, 85, 95, and 102°. None of these is far beyond the "normal" range. Similarly his illustrations of left axis deviation in Fig. 21 may be calculated as: 55, 40, 23, 20, and 25° in I and II; or: 55, 40, -25, -28, -38° in Leads II and III, showing that an unchallenged alternative method of interpretation may introduce a fifty degree discrepancy. It is suggested that in every out-of-phase record the method of calculation be indicated, and better still, if homologous points are available, the axis offered for consideration should be carefully designated as, e. e.:  $R_1-R_2$ ,  $R_1-R_3$ ,  $R_3-Q_1$ , etc.

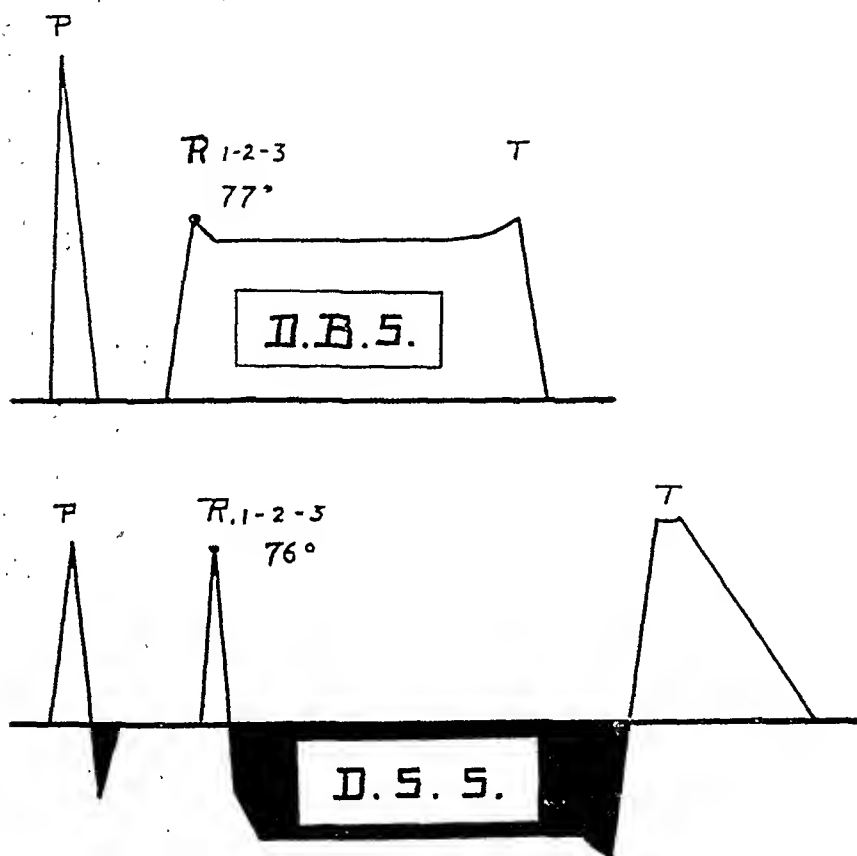


Fig. 2.—Electrical axes plotted at about 0.01 second intervals throughout the cycle, with negative angles below the base line. Upper curve: dog with deep bulbospiral muscle infarct; lower curve: another dog with deep sinospiral muscle injured. Note that in both the R-wave axes are identical but the S-T axes are displaced in opposite directions (although each lesion is on the left side of the heart).

3. *The Indifference of the R-wave to Peripheral Lesions.*—The inference is inescapable that, if the electrical axis has any significance whatsoever, its behavior throughout the entire cycle will be more instructive than at any one point. In Fig. 2 it is evident that the axis (of R) is identical in two dogs following acute infarctions of the deep sinospiral muscle in one heart and of the deep bulbospiral in the other, although other regions of the axis are strongly contrasted. (Incidentally, this observation refutes the suggestion<sup>21</sup> that the S-T displacements of infarction are associated with rotation of the heart itself



because the visible absence of gross rotation is here corroborated by the internal evidence of an unchanged R-axis. This figure does show that the one region of the electrical axis usually inspected may be indifferent to gross pathology known to exist beyond the major branches of the bundle of His.

4. *Apparatus*.—Evaluation of the electrical axis for an entire cycle (at intervals of 0.005 to 0.010 second) is arduous without simultaneous records by two or more balanced galvanometers (having identical string periodicity, and circuits of *equal resistance* to avoid shunting deformity of the records), focussed on a single camera with a common time marker to avoid parallax. In reading the data an accurate measuring instrument is desirable.

It is significant that de Waart,<sup>22</sup> using three simultaneous leads has reported a remarkably narrow range of normal values for the R-axis in the *Macaca irus*, between 50 and 75° with an average of about 70°. We have been able to confirm his figures in monkeys of another species (*Macacus rhesus*), and we have observed a similarly restricted range for the R-axis in normal dogs. It is our hope that an understanding of the human electrocardiogram may be extended by a rigorous adherence to precautions such as are outlined in this paper.

#### SUMMARY AND CONCLUSIONS

I. The wide variation in the values accepted as normal for the electrical axis is ascribed, in large measure, to improper and inconsistent treatment of the data.

1. In approximately three-fourths ( $74 \pm 5$  per cent) of one hundred recently published electrocardiograms the R-peaks of the standard leads are out-of-phase. In such cases there exists no satisfactory method for calculating this axis.

2. When the R-peaks are out-of-phase (so that  $E_2$  is not the sum of  $E_1 + E_3$ ), each R may have an axis of its own that differs some 50 to 100° from the others.

3. In such cases, the arbitrary selection of any two leads from which to calculate an axis produces some unreal number that may differ 50° from that derived from another person's interpretation of the same tracing. This accounts for a considerable part of the reported variation.

II. It is also probable that too much has been expected of the R-wave and its axis.

1. It must be remembered that the axis can not reflect conditions that exist at right angles to the frontal plane when only standard leads are employed, because secondary electrodes record electrical events best when in a parallel direction and least of all when perpendicular. Since much of the Purkinje system deviates from the frontal plane, preferential and "silent" areas are created by the orientation of the very electrodes used to explore them.

2. Furthermore, the peak of the R-wave, together with its electrical axis, may be entirely unresponsive to experimental infarction of the deep bulbospiral or deep sinospiral muscles, although these lesions markedly affect the axis in a *later* portion of the cycle.

3. Apparently there is no close correlation (and no good reason to expect such a relation) between the R-axis and peripheral lesions not involving the main branches of the bundle of His.

## REFERENCES

1. Einthoven, W., Fahr, G. E., and de Waart, A.: Ueber die Richtung und die manifeste grösse der Potentialschwankungen im menschlichen Herzen und über den Einfluss der Herzlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. 150: 275, 1913.
2. Millikan, R. A., and Mills, J.: Electricity, Sound and Light, Boston, 1908, Ginn and Company, p. 15.
3. Trendelenburg, W.: Untersuchungen über die Aktionsströme des menschlichen Herzens. V. Die Bestimmung der elektrischen Achsen des Herzens (Elektrotopographie), Ztschr. f. d. ges. exper. Med. 92: 41, 1933.
4. Kahn, R. H.: Beiträge zur Kenntnis der Elektro-Kardiogramms, Arch. f. d. ges. Physiol. 126: 197, 1909; 129: 291, 1909.
5. Fahr, G. E.: Simultaneous Records of Heart Sounds and the Electrocardiogram, Heart 4: 147, 1912; Arch. Int. Med. 27: 126, 1921.
6. Williams, H. B.: On the Cause of the Phase Difference Frequently Observed Between Homogenous Peaks of the Electrocardiogram, Am. J. Physiol. 35: 292, 1914.
7. Lewis, Sir Thomas: Mechanism and Graphic Registration of the Heart Beat, 1925, Chapter 8, Paul B. Hoeber.
8. Meek, W. J., and Wilson, H.: The Effect of Change in Position of the Heart on the QRS Complex of the Electrocardiogram, Arch. Int. Med. 36: 614, 1925.
9. Robb, J. S., Greene, W., and Robb, R. C.: The Significance of the Peripheral Distribution of the Purkinje Fibers, J. Tech. Methods and Bull. I. A. M. M. 1937. In press.
10. Katz, L. N., Bohning, A., Gutman, I., Jochim, K., Korey, H., Oeko, F., and Robinow, M.: Concerning a New Concept of the Genesis of the Electrocardiogram, AM. HEART J. 13: 17, 1937.
11. Waller, A. D.: Various Inclinations of the Electrical Axis of the Human Heart. Part IA. The Normal Heart: Effects of Respiration, Proc. Roy. Soc. London, S. B. 138, B: 49, 1914.
12. Carter, E. P., Richter, C. P., and Green, C. H.: A Graphic Application of the Equilateral Triangle for Determining the Electrical Axis of the Heart in the Human Electrocardiogram, Bull. Johns Hopkins Hosp. 30: 162, 1919.
13. Pardee, H. E. B.: Determination of Ventricular Preponderance, Arch. Int. Med. 25: 683, 1920.
14. Proger, S. H., and Davis, David: The Significance of Axis Deviation in the Human Electrocardiogram, Arch. Int. Med. 45: 974, 1930.
15. White, P. D.: Heart Disease, New York City, 1937, The Macmillan Company.
16. Wilson, F. N., McLeod, A. G., and Barker, Alex. J.: The Accuracy of Einthoven's Equation, AM. HEART J. 7: 203, 1931-32.
17. Carter, J. Bailey: The Fundamentals of Electrocardiographic Interpretation, Baltimore, 1937, Charles C. Thomas.
18. Pardee, H. E. B.: Clinical Aspects of the Electrocardiogram, New York, 1933, Paul B. Hoeber.
19. Jones, H. W., and Roberts, R. E.: Electrical Axis of Heart as an Indicator of Changes in Ventricular Predominance, Quart. J. Med. 23: 67, 1929.
20. Herrmann, G. R., and Wilson, F. N.: Ventricular Hypertrophy: A Comparison of Electrocardiographic and Post-mortem Observation, Heart 9: 91, 1922.
21. Abramson, D. I., Shookhoff, C., and Fenichel, N. M.: A Study of Variations of the RS-T Segment in Experimental Ventricular Trauma, AM. HEART J. 17: 174, 1936.
22. De Waart, A., Storm, C. J., and Koumans, A. K. J.: Ligation of the Coronary Arteries in Javanese Monkeys, AM. HEART J. 11: 676, 1936; *ibid.* 12: 70, 1936; *ibid.* 12: 184, 1936.
23. Dieuaide, F. R.: The Determination and Significance of the Electrical Axis of the Human Heart, Arch. Int. Med. 27: 558, 1921.

## THE SYMBALLOPHONE: A MODIFIED STETHOSCOPE FOR THE LATERALIZATION AND COMPARISON OF SOUNDS\*

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IT IS well known that the direction from which a sound comes is determined chiefly by the difference in time required for the sound waves to reach the tympanic membrane of the two ears and register in the brain as sound. The variation in intensity of the sound reaching the two ears is probably of lesser importance in determining the source of external sounds.

We have made use of these principles in the construction of a new type of stethoscope for comparison of two areas over the heart and lungs. Preliminary observations indicate that differences in timing of sounds from the two areas compared can be used to determine the point of origin of sounds and the direction of propagation. This information should be of practical importance in clinical medicine. The principles may also be applied in other fields where the point of origin of sounds and the direction of travel of sound are of interest.

In 1910, Muralt<sup>1</sup> devised a stethoscope which permitted the physician to listen simultaneously to two areas over the lungs. This stethoscope consisted of two endpieces or acoustic bells with tubes running from each bell to both ears. It is apparent from his illustrations that the crossed tubes to the opposite ears were equal in length to the tubes passing directly from one endpiece to the ear on the same side. Sounds originating in one endpiece reached both ears simultaneously. More recently, Fröschels<sup>2</sup> suggested the use of a "differential stethoscope" which is essentially a pair of endpieces each connected to the ear by a single tube and each passing through an X or four-way connection which permits either an ipso- or contralateral course of the sound to each ear. This instrument was devised to study the sounds produced in the vocal cords in the detection of laryngeal paralysis.

Nicolai<sup>3</sup> devised a "stereostethoscope" to detect differences in sounds originating in the two mandibular joints, and suggested its use in other fields of clinical medicine. This instrument consisted of two endpieces with simple tubes passing directly to the ear on the same side, as shown in Fig. 1 A. Hantsehnann and Nicolai<sup>4</sup> reported that this instrument was of value in the study of cardiac and pulmonary disease.

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Read before the American Heart Association, Section for the Study of Cardiac Diseases, at Atlantic City, N. J., June 8, 1927.

In 1935, Hawthorne<sup>5</sup> described the use of the differential (double) stethoscope, a type similar to the one described by Nicolai.<sup>3</sup> Alison<sup>6</sup> had described this type of stethoscope, in 1858, and gave a report on its use in 1859.

The symballophone, or sound-comparing stethoscope, which we have devised is illustrated in Fig. 1 *B*. The essential point of difference from Muralt's stethoscope is the introduction of a *longer connecting tube* from each endpiece to the *opposite* ear than the direct tube passing to the ear on the same side. The difference in length between the direct and crossed tubes is not a fixed distance; but we have found that if the crossed tubes are only 3 cm. longer than the direct

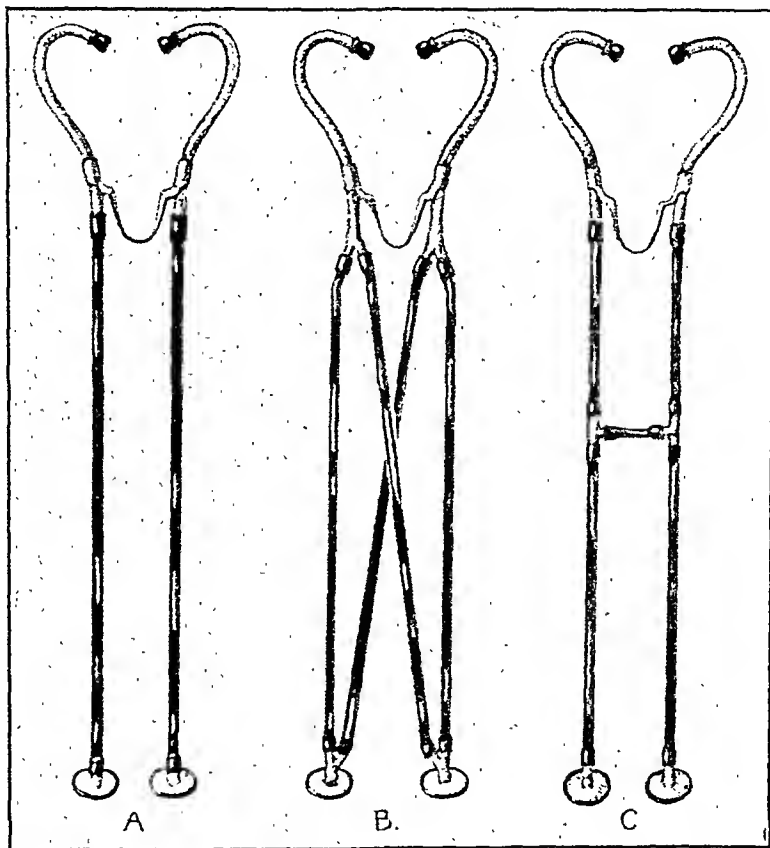


Fig. 1.—A, Nicolai's stethoscope; B, the symballophone showing the arrangement of tubing for a simple model. The diagonal tubes are longer than the lateral tubes, and the bore of the crossed tubes is reduced. C, a variation of B, but impractical.

tubes the device will serve its purpose. If the crossed tubes are about 15 to 20 cm. longer than the direct tube, the lateral deflection of the point of origin of the sound appears to be maximal. If the caliber of the crossed tubes is less than that of the direct tubes, the difference in the intensity of the sound reaching the two ears further enhances the ability to *lateralize* the source of the sound. Empirically, if the crossed tubes have a bore three-fourths that of the direct tubes, the results are best. Further study is in progress to determine the optimal differences in caliber and lengths of tubing. Psychological studies show definitely that with the use of the symballophone dissimilar sounds arising from any two points to be compared give an illusion which seems to lateralize

the quality being investigated. If one endpiece of the instrument is used alone, the impression of lateralization is enhanced.

Modifications of the arrangement of tubes may be devised. Fig. 1 *C* shows one of these modifications which has a single connecting tube between the two direct tubes, each going from the endpiece to the ear on the same side. The connecting or crossed tube permits sound waves to pass in either direction in going to the opposite ear, and if the length of the crossed tube is approximately 3 cm., the comparison of sounds may be made to permit lateralization. However, confusion may arise because sound waves may travel readily up or down the direct or vertical tubes. Refinements may be added to eliminate the long or diagonal tubes shown in Fig. 1 *B*. Stopcocks may be inserted near the endpieces for this purpose. If the two endpieces are then placed in juxtaposition over the heart or lungs, the instrument will serve as a familiar binaural stethoscope.

The theoretical basis for the construction of the comparing stethoscope may be stated briefly as follows:

Sound travels in air at the rate of 330 meters per second or 3.3 cm. per 1/10000 second. The rate in sea water is approximately 1454 meters per second or 14.5 cm. per 1/10000 second. The rates for solids vary from 3000 to 5000 meters per second. The auditory apparatus is capable of detecting very small differences in time of reception of sounds. Sounds which arrive 0.000032 second apart can be perceived. If the crossed or diagonal tubes shown in Fig. 1 *B* are 3 cm. longer than the straight or direct tubes, any sound traveling by air at the rate of 330 meters per second and originating at one of the endpieces will reach the homologous ear through the straight or direct tube 0.0001 second before it reaches the opposite ear. This difference in the time of reception in the two ears is three times the minimum time necessary for differentiation and will create the impression that the sound arose from the side which registered the sound first. From our observations, sounds originating in the blood stream heard at one endpiece and passing to both ears (in different times) register before those received at the other endpiece reach the ears. Theoretically, this should not be possible if the sounds heard are propagated from their points of origin in a fluid or solid medium. In the practical use of the comparing stethoscope, it is apparent that the sounds heard over vessels (murmurs) travel at a rate approximating the rate of travel of the pulse wave and not at the rate at which sound would travel through a liquid or solid medium. Clinicians will appreciate the fact that the systolic thrill over the carotid arteries in aortic stenosis is simultaneous with the systolic murmur at that point, and that the thrill is simultaneous with the pulse wave which is approximately one-twentieth of a second after the contraction of the ventricles. It is probable that the murmurs heard along their path of propagation are produced by vibrations in the blood or walls of the

vessels associated with eddies in the blood which are continued for a considerable distance beyond the point where faults in streamlining initiate them. Further studies with accurate registration of the propagation of sound impulses are being made.

Tests for the practical use of the instrument have shown that localization of the side from which the sound appears first is readily determined. Among a class of 50 senior medical students, no errors were made. In addition to the ability to detect differences in timing, differences in pitch and intensity can be appreciated by the quick comparison made possible by this device.

It is suggested that this instrument will also be of use in studying the following conditions: injury of one recurrent laryngeal nerve; unequal volume and timing of pulsations in peripheral arteries; asynchronous beating of the heart of twins in utero; unequal contractions of muscles; peristaltic sounds in the large intestine; and possibly in other clinical conditions where differences in timing and intensity of sounds are observed.

The device should be of great practical value in comparing sounds associated with respiration over two sides of the chest. Differences in timing, pitch, and intensity are easily detected, and the location of râles, friction sounds, and other abnormal sounds are readily localized.

By the use of the comparing stethoscope, the interest of the clinician in sounds is quickened. Sounds may be said to take direction and to be "alive." To listen over a vessel in which the blood is flowing and carrying vibrations which we interpret as sound, conveys a sensation of fluid in motion which is not produced by listening to the murmur with the familiar binaural stethoscope.

The illusion which is created by the devices of increasing the length and decreasing the bore of tubes passing to the opposite ears from two endpieces is of value in clinical medicine and in other fields where a comparison of sounds is desirable. One may compare two areas for compound differences in qualities which may be analyzed separately. The direction in which sound is traveling can be determined. This is of practical importance in the case of murmurs.

Further psychological studies are in progress. No permanent model can be constructed until all the facts are known. From an empirical standpoint, the device marks a signal advance among the aids in clinical diagnosis.

#### REFERENCES

1. Muralt, L. V.: Zur Kenntnis der symmetrisch fortgeleiteten Rasselgeräusche, *Beitr. z. Klin. der Tuberk.* 16: 121, 1910.
2. Fröschels, Emil: Ein Differenzstethoskop, *Med. Klin.* 30: 1099, 1934.
3. Nicolai, L.: Über das "Stereostethoskop," *Klin. Wchnschr.* 15: 91, 1936.
4. Hantschmann, L., and Nicolai, L.: Erfahrungen mit dem "Stereostethoskop" in der inneren Medizin, *Klin. Wchnschr.* 15: 92, 1936.
5. Hawthorne, C. O.: Differential (Double) Stethoscope, *Irish J. M. Sc.* 7th series, no. 110, p. 49, 1935.
6. Alison, S. Scott: *Med. Times and Gaz.*, n.s. 19: 7 and 28, 1859.

## A QUANTITATIVE STUDY OF CUTANEOUS CAPILLARIES IN HYPERTHYROIDISM\*

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THE cutaneous circulation, in addition to serving the function of local tissue metabolism, assists in the dispersion of heat from the body. Disturbance of the cutaneous circulation is, therefore, to be expected in conditions that alter the total metabolism. This correlation occurs in fever. It may be expected in hyperthyroidism, but we have found no quantitative demonstration of its occurrence in this condition.

By capillary microscopy, first described by Lombard,<sup>1</sup> it is possible to study directly some of the vessels of the skin. The following calculation, based upon figures obtained from the dorsum of the hand, indicates how few of these vessels are visible. The length of a capillary loop approaches 0.82 mm. and its width 0.008 mm. The total number of visible loops per square cm. is approximately 8,100. Hence the visible capillaries per square cm. would contain 0.334 c.mm. of blood. As the surface area of a man of 80 kgm. is approximately 1.8 sq. meters, such a man would have, assuming the same capillary distribution, about 6 c.c. of blood in his visible capillaries. In addition, the subpapillary venous plexus is more or less visible. On the average, the individual limbs are 0.03 mm. wide and approximate an arrangement of superimposed circles with centers 0.3 mm. apart. By a similar calculation, the total amount of blood contained in the subpapillary venous plexus of the entire body would be about 16.9 c.c., making a total for the visible vessels of the skin approaching 22.9 c.c. These figures are subject to correction for variation in size and distribution of the vessels in different skin areas. We found that vessels of the subpapillary plexus over the face and neck are distinctly wider and the total number of capillaries per sq. cm. distinctly greater than the averages given here. The vessels of the plexus over the trunk are narrower and the distribution scantier. In spite of these observed variations the approximation is useful until better figures are available.

That this amount of blood is sufficient to account for the color of the skin may be shown by the following procedure: From the above figures the amount of blood in one sq. cm. of skin is found to be about 1.3 c.mm. To each of two glass cylinders, having an area at the base of 15.9 sq. cm., were added 2 c.c. of distilled water. One of these cylinders was placed over the skin and the skin color observed through a peephole. The color

\*From the Robinette Foundation, the Medical Clinic, the Endocrine Clinic, and the Pepper Laboratory of the Hospital of the University of Pennsylvania.

†Atwater Kent Fellow in Medicine.

exactly matched that of the surrounding skin. Pressure was applied by the cylinder to the skin and the skin blanched.

To the second cylinder 20 c.mm. of whole blood were added. (We estimated 1.3 c.mm. of blood per sq. cm. of skin. As the base of the cylinder was 15.9 sq. cm. a similar area of skin would contain 20.67 c.mm. of blood. The contents of the cylinder were then comparable to the amount of blood in the visible vessels.) With this container the above procedure was repeated as with the cylinder containing only distilled water. Seen through the peephole the skin was definitely darker than the surrounding skin. When pressure was applied the color matched that of the surrounding skin.

The visible circulation is therefore adequate to explain the color of the skin but we believe it inadequate to account for the heat loss occurring from the skin. However, this visible circulation shows alterations which are probably typical of those occurring in the entire cutaneous circulation.

Four different kinds of observations could be made to study these changes: (1) speed of flow; (2) per cent of total capillaries showing flow; (3) width of vessels; (4) number of capillaries normally open as compared with the total number open in the same area under conditions of maximal dilatation. This fourth method we considered would supply quantitative data with a minimum of subjective error, and was therefore the one chosen.

Most observers who, in capillary microscopy, have used the dorsum of the hand have found little change in the number of capillaries under varying experimental conditions. Lewis<sup>2</sup> indeed states that all the capillaries in this area are constantly open. Bordley,<sup>3</sup> on the other hand, finds a varying change in the number of open capillaries in the skin over the tibia. We have found that on the face, neck, and hands in exposed areas most or all of the capillaries are open constantly, but over the arms and other areas protected by clothing that only a fraction of the total number are open.

#### METHOD

Patients with hyperthyroidism were obtained from the endocrine clinic or from the wards of the University Hospital. All had a definite diagnosis of hyperthyroidism and an elevated basal metabolic rate without subsequent treatment preceding our study. As controls we used patients from the wards or dispensaries in whom no vascular nor metabolic disturbance could be found. All cases when studied had been in the hospital at least two hours. A thyroid case and a control were examined alternately throughout the study, which was started November, 1936, and completed May, 1937.

The skin area studied was on the forearm, midway between the wrist and the elbow. The arm was placed at the level of the sternum. An area of approximately 2 sq. mm. was marked by inking a circular die and



pressing it gently on the skin. The exact area varied somewhat with the tension and elasticity of the skin and the tendency of the ink to run slightly, but when once marked was constant for the duration of the experiment.

The method of capillary microscopy was that previously described by one of us.<sup>4</sup> The area was covered with cedar oil. Light from a 500-watt bulb was cooled by passing it through water and directed upon the area. Observations were made using a microscope with a magnification of  $\times 32$ . The number of visible capillaries was recorded.

At a distance of 1 cm. from the marked circle histamine 1:1,000 was pricked into the skin and, at one-minute intervals, the number of visible capillaries was counted. The maximum number was recorded.

### RESULTS

Sixteen cases of hyperthyroidism are reported, with fourteen controls. Before histamine is pricked into the neighboring skin a number of capillaries can be counted. Because the capillaries pass almost at right angles to the skin surface only their tips are visible, appearing as small loops or hooks. In the patient with hyperthyroidism many more capillaries can be seen than in the control, as a rule. After histamine there is a striking increase in the number of visible capillaries in the control. After histamine in the patient with hyperthyroidism there is a relatively slight increase in the number of visible capillaries. It is obvious that the increase after histamine is marked in the control and negligible in the patient with hyperthyroidism. It is to be noted, however, that the patient with hyperthyroidism has a large number of capillaries visible before histamine.

The change in the number of visible capillaries in a normal subject before and after histamine is illustrated in Fig. 1. Photographs were made using an Ultrapak, Leitz camera, and arc lamp. The exposure was one second. The intensity of light was identical for both exposures. In the first film only two capillaries show as tiny black dots close to the free end of the upper hair. At this low magnification the capillary tips show as dots. The general field is quite light. The stubs of two hairs show. The ink marking has been trimmed away in the photograph except for a small dab of ink which has run along the roots of the hairs. The second photograph was taken four minutes after histamine. Macroscopically the marked circle lies in the flare area. In the photograph the entire field is much darker. The two capillaries previously seen are still present and many others have appeared. Short lengths of the subpapillary venous plexus are visible. In a photograph made at a single focus their continuity with each other cannot be demonstrated. Similarly, all capillaries are not in focus and absolute counts cannot be made from photographs. The lower hair has been swept out of the field and the upper is bent slightly downward and is more clearly in focus.

The results of the entire series are charted in Fig. 2. The increase averages 120 per cent for the controls, with a range of 62 to 220 per cent. For the patients with hyperthyroidism the average increase is 16 per cent with a range of 0 to 82 per cent. The patient designated

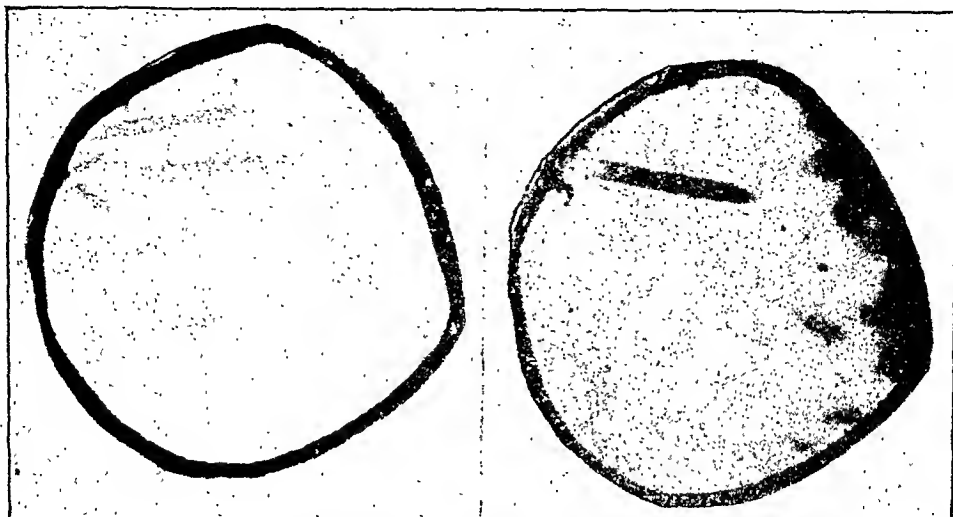


Fig. 1.—Photomicrographs taken of the extensor surface of the forearm in a normal subject. Area of approximately 2 sq. mm. The photomicrograph on the left shows the normal appearance. Only two capillaries are visible as dots near the free end of the upper hair. The photomicrograph on the right shows the same area after histamine. Numerous capillaries and branches of the subpapillary venous plexus are visible and the entire field is darker. For further details see text.

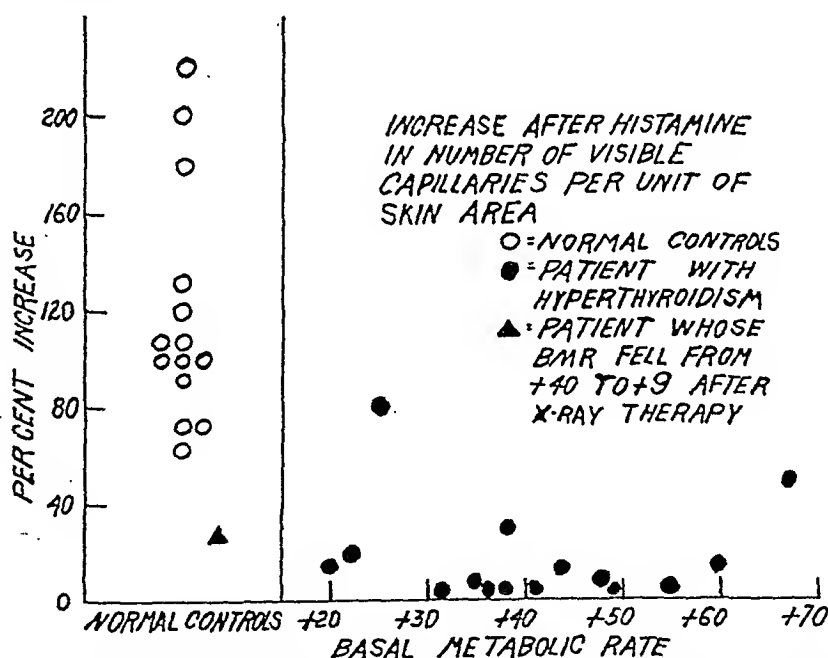


Fig. 2.—Chart showing the relation between basal metabolic rate and per cent increase in capillary counts after histamine in normal controls and in hyperthyroid subjects.

by a triangle is not included in the series. She was a patient, formerly hyperthyroid, whose basal metabolic rate had fallen to normal following roentgen treatment but who retained the capillary behavior similar to that which we found in hyperthyroid patients.

The capillary counts are not given because (1) for reasons previously stated the size of the area studied was not exactly the same in different

patients and (2) conditions of skin texture affect visibility and hence the count. In the controls before histamine the average count was 16, ranging from 8 to 24, while in the patients with hyperthyroidism the average was 23, with a range from 8 to 42.

#### DISCUSSION

The volume of blood in the visible vessels is too small to be important in heat loss. If, however, these vessels reflect the behavior of all the minute vessels of the skin, of which they form a part, then their behavior becomes significant. The evidence presented suggests that in the hyperthyroid state most of the cutaneous capillaries are open, as might be expected to provide for the heat loss. Such increased filling of the peripheral bed, if unaccompanied by constriction elsewhere, would necessitate an increase in blood volume. Chang<sup>5</sup> has reported an increase in blood volume in hyperthyroid states.

The degree of cutaneous dilatation is not closely correlated with the basal metabolic rate, for patients with minimal change of capillary count in response to histamine had basal metabolic rates ranging from plus 32 to plus 55, whereas two patients with the highest basal metabolic rates (plus 60 or over) had increased counts after histamine in one case by 50 per cent and in the other by 16 per cent. This is in accord with the findings on blood volume, for the increase of the basal metabolic rate is reported as not proportional to the increase in the blood volume.

#### SUMMARY

Capillary counts were made in an area of approximately 2 sq. mm. in normal controls and in hyperthyroid patients. The area chosen was the extensor surface of the forearm midway between the elbow and wrist. Capillary counts were made in the same area before and after pricking histamine into the skin. While absolute counts in different patients cannot be directly compared, per cent increase in the same patient is considered significant. Of the sixteen hyperthyroid patients, the increase averaged 16 per cent, of the fourteen controls, 120 per cent.

It is suggested that in the hyperthyroid state an increased dilatation of the cutaneous circulation assists in the loss of heat by the body. The degree of dilatation is not related quantitatively to the height of the basal metabolic rate, however.

#### REFERENCES

1. Lombard, W. P.: The Blood Pressure in the Arterioles, Capillaries, and Small Veins of the Human Skin, *Am. J. Physiol.* 29: 335, 1912.
2. Lewis, T.: Regulation of Blood Flow Through Capillaries of Human Skin, *Heart* 13: 1, 1926.
3. Bordley, J., Grow, M. H., and Sherman, W. B.: Intermittent Blood Flow in Capillaries of Human Skin, *J. Clin. Investigation* 14: 702, 1935.
4. Griffith, J. Q., Jr.: The Frequent Occurrence of Abnormal Cutaneous Capillaries in Constitutional Neurasthenic States, *Am. J. M. Sc.* 183: 180, 1932.
5. Chang, H.: Blood Volume in Hyperthyroidism, *J. Clin. Investigation* 10: 475, 1931.

## THE TREATMENT OF SCLERODERMA BY MEANS OF ACETYL BETA METHYL CHOLINE CHLORIDE (MECHOLYL) IONTOPHORESIS\*

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THE object of this report is the presentation of a new method of treatment of the condition commonly known as scleroderma. A survey of the literature makes it apparent that this is a diagnostic term which is rather loosely used. European writers for the most part describe scleroderma verum as a disease primarily involving the torso and proximal parts of the extremities. Acrosclerosis is the term applied to a condition manifesting similar skin changes but primarily affecting the distal parts of the extremities and always associated with vasomotor disturbances. Sellei<sup>1</sup> attempted in 1934 to differentiate between these two conditions. In this country the term scleroderma is customarily used to include both processes. Brown, O'Leary, and Adson<sup>2, 3</sup> in their reports of 1930 group their cases of acrosclerosis under this heading.

Sellei believes that the true scleroderma, as he classifies it, has a definite etiology in deficient pancreatic function and he reports almost 100 per cent success in treating these cases over a period of two years with extracts of pancreas, muscle, and liver. Other writers<sup>4-10</sup> in discussing treatment usually refer to those cases in which a vasomotor disturbance is present and more than one-half of the recommended therapy is based on an attempt to improve the circulation to the skin. The arterial sympathectomy of Leriche and the ramisection and ganglionectomy of Brown and Adson are attempts in this direction. Another group of workers have approached this problem from the viewpoint of possible endocrine pathology and consider that the vasomotor disturbances and the calcium imbalance which are present are due to dysfunction of the adrenal, pituitary, thyroid, or parathyroid glands. Bernheim and Garlock,<sup>11</sup> and Leriche and Jung<sup>9, 10</sup> have reported some success following partial parathyroidectomy. Osler<sup>12</sup> reported a series of eight cases improved by the use of thyroid extract and one of the authors of this paper has seen a case improve during the use of anterior pituitary therapy.

It is apparent that since success has been reported following these various forms of therapy in all probability the cases treated had different etiologic backgrounds and it may be proven in the future that the pathologic condition of which we are speaking is a syndrome pos-

\*Read before The American Heart Association, Section for the Study of the Peripheral Circulation, at Atlantic City, N. J., June 7, 1937.

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sibly resulting from several causes. In the experience of the authors, however, improvement with any previous treatment has been rare. None of the patients reported in this paper had shown even moderate improvement prior to their appearance, although their treatment included a wide variety of therapy such as noted below.

We shall not attempt in this paper to discuss the possible mechanisms involved in the production of this syndrome. The field has been admirably covered by Lewis and Landis<sup>12</sup> and more recently by Prinzmetal.<sup>14</sup> They have demonstrated the circulatory mechanics involved in scleroderma. Removal of the sympathetic control of the peripheral circulation by surgery in cases of a Raynaud's syndrome without scleroderma results in the release of spasm and an abundant blood supply. If scleroderma has produced a mechanical blocking of the vessels due to the tension of the leathery skin, vasodilatation by removal of sympathetic control is impossible.

It has been our experience that the relief of spasm by mecholyli iontophoresis in Raynaud's disease without scleroderma has been of only temporary value. However, as reported in this paper, in scleroderma there appears to be a softening of the thickened skin as well as a vasodilatation.

We are reporting herein a series of thirty-four patients with scleroderma who have been studied by the staff of the Vascular Clinic at the New York Post-Graduate Hospital. Of these all but one are patients with vasomotor disturbances and therefore should be classified according to Scler as arosclerosis. The first patient in this series was seen in April, 1933, and the majority of the patients were followed throughout 1935 and 1936. Table I shows the distribution of these cases as to age,

TABLE I  
SCLERODERMA IN 34 PATIENTS

|                              |  |
|------------------------------|--|
| AGE                          | Eight years to 61—Average—37.9 years                     |
| SEX                          | Eight males, (23.5 per cent)—26 females, (76.5 per cent) |
| BIRTHPLACE                   | America—25<br>Russia—3<br>Italy—3<br>Germany—3           |
| DURATION OF SCLERODERMA      | Three months to 180 months—Average—59.3 months           |
| COMPLICATING RAYNAUD'S       | 32 definite—2 doubtful                                   |
| AVERAGE DEGREE OF DISABILITY | Av. ++ to +++<br>Range (+ slight to ++++ complete)       |
| BLOOD PRESSURE               | 90/? to 164/92   |

sex, nationality, duration of the illness, and the average degree of disability. Twenty-six (76.5 per cent) were in females, and this corresponds to the sexual ratio of Raynaud's syndrome. The average age of the patients treated was 37.9 years, the extremes were eight and sixty-one years. This approximates the usual age incidence of vasospastic

diseases. The average duration of the history of sclerodermal changes was 59.3 months, the extremes were nine months and fifteen years. Occupation apparently had little or nothing to do with the etiology. Hands were much more frequently involved than feet and disability ranged from total incapacity for activity to a slight stiffness of the fingers. Capillary examinations in most individuals in which the skin changes permitted visualization of the vessels, showed large dilated loops typical of a Raynaud's syndrome. Seventeen of the patients had developed trophic ulcers. None had gangrene involving more than two square centimeters of surface area.

The use of various choline derivatives, especially acetyl beta methyl choline chloride (mecholy<sup>\*</sup>) in the treatment of certain peripheral vascular diseases including preliminary data dealing with scleroderma, has been previously reported from our clinic.<sup>15, 16, 17</sup> It was noted that in some patients there was a definite softening of the thickened skin following the prolonged use of this substance by iontophoresis. This drug is absorbed if used in the form of a solution on a bandage over the affected areas to which is applied the positive electrode of a galvanic battery. Sufficient of the choline (whether changed or unchanged) may be absorbed to produce systemic reactions during the course of the treatment, such as sweating, increased salivation, a drop in blood pressure, and frequently increased intestinal peristalsis. In the treatments reported in this study a one-half of one per cent solution of the drug was applied to the asbestos bandages, and about twenty milliamperes of current were allowed to flow for twenty to thirty minutes during each treatment. Locally a marked vasodilatation occurs so that after the removal of the bandage an area of rubor persists for several hours which is accompanied by sweating.

The technique has been described in detail in the above references.<sup>15-17</sup> One observation is worthy of note. The negative electrode is usually placed on the back of the patient. This pad is well moistened with tap water and is applied firmly to the body. Among the patients with scleroderma slight negative burns were frequently noted; while in treating patients for other conditions they seldom occurred. It would seem that the skin of the former group is more sensitive.

An attempt was made to treat parts showing marked changes in the skin typical of the pathologic condition. Because of technical difficulties certain areas on the face, neck, and trunk were left untreated. It was impossible to treat extensive lesions at one time and in patients having large areas involved more frequent treatments were given. The solution was applied to not more than two extremities on one day. Daily applications were given in as many cases as possible but the majority of our patients received treatment two or three times a week.

<sup>\*</sup>The acetyl beta methyl choline chloride (mecholy<sup>l</sup>) used in this study was supplied through the kindness of Merck & Co., Inc., Rahway, N. J.

These patients have received from 6 to 165 treatments. Little, if any, results were noted with less than 10 treatments. Some patients stopped after 30 or 40 treatments because the degree of improvement was satisfactory. It would seem from our observations that probably 50 treatments would be necessary in most instances and in the advanced forms of the disease many more before a satisfactory result can be obtained.

Patients in our series had previously received many forms of treatment with little or no success. Case 21, showing marked improvement with mecholyl iontophoresis, had had a parathyroidectomy and a unilateral thyroidectomy a year previously with very slight improvement. Cortical extract administered for two years had also been ineffectual. Case 23 had had a bicervical sympathectomy, triple typhoid vaccine, tissue extract, and glycine without results. It was interesting to note that she had been given ergot in spite of the fact that she had a Raynaud's syndrome. She was skin-sensitive to mecholyl and therefore this form of therapy could not be used. Case 26 also received ergot. In addition she was treated with intravenous sodium citrate, typhoid vaccine and diathermy, and a sympathectomy. Two cases died cardiac deaths before sufficient therapy could be administered. One had mitral stenosis and was fibrillating, and the other had arteriosclerotic heart disease. One other patient (Case 18) in our series died from Addison's disease before any treatment was instituted for the scleroderma. Two of our patients showing a pronounced Raynaud's syndrome and excessive arsenic secretion in the urine were given a diet low in arsenic and injections of sodium thiosulfate without improvement of the scleroderma. One of these patients has just started mecholyl treatment. The other has received over 100 treatments with very marked improvement (Case 19).

Our criteria for classifying patients as "markedly improved" are as follows: 1. Restoration of practically normal function. 2. Healing of existing ulcers. 3. Softening and loosening of the skin. 4. Return of sweating and hair to the affected areas. 5. Increased visibility of capillaries (not always noted).

TABLE II  
RESULTS OF MEC HOLYL IONTOPHORESIS TREATMENT OF 27 PATIENTS  
WITH SCLERODERMA

| IMPROVEMENT                | NUMBER OF TREATMENTS      | REMARKS  |
|----------------------------|---------------------------|--|
| Marked—9 patients          | 33 to 165<br>Average 81.0 | No other form of therapy                                 |
| Moderate—7 patients        | 10 to 88<br>Average 32.0  | 2 received tissue<br>Extract No. 568<br>1 died pneumonia |
| Total improved—16 patients |                           |  |
| Slight or none—11 patients | 6 to 20<br>Average 11.8   | 1 atypical<br>1 result unknown<br>1 by mouth             |

Patients classified as "moderately improved" have shown a definite approach toward the above listed criteria. Those showing only slight response to therapy have been included in the unimproved group. Table II summarizes the results of treatment. All cases receiving 30 or more treatments showed either marked or moderate improvement. Cases showing no improvement were noted to have received 20 or fewer treatments. An atypical case did not respond to this form of therapy.

The following two typical cases of scleroderma are briefly summarized. They both showed marked improvement to mecholyl iontophoresis.

**PATIENT L. C.—Present Illness:** A female, aged fifty years of Italian parentage, was first seen on March 3, 1934. She had complained of stiff and painful fingers and toes for five years with inability to do any form of work. After exposure to cold they would turn blue and become painful. This would disappear after five to ten minutes in a warm room. During the last two years the skin of the face had become stiff and motion of the jaws was limited.

**Past History.**—There was no illness. She had had three normal pregnancies. Menopause had occurred six months before her first clinic visit. She has eaten 1½ pounds of rye bread daily for years.



Fig. 1.

Fig. 2.

Fig. 1.—Patient L. C., maximum finger flexion before treatment. Marked trophic changes are present.

Fig. 2.—Patient L. C., maximum finger flexion after 170 treatments with mecholyl iontophoresis.

**Physical Examination.**—The patient was a well-nourished, slightly obese Italian woman appearing about her stated age. The face was expressionless and wax-like. The nose was pinched and the upper lip almost immobile. The fingers were stubbed, the distal phalanges being shortened. Motion in all finger joints was nearly zero. Trophic changes were present over the tips of the fingers and the nails were markedly deformed. No ulcers were present when she was first examined. The toes showed slight changes of a similar nature. The skin was very tense and felt like leather.

**Capillary Microscopy.**—The vessels were seen with difficulty, and were reduced in number. There were no dilated loops. There was a moderate rate of blood flow. The complete physical examination and routine laboratory tests were normal.

**Treatment.**—Nineteen injections of acetyl choline 100 mg. each were given in five months with very slight improvement. From September, 1934 to May, 1937, she was given 170 treatments of mecholyl iontophoresis. Improvement was marked. The patient could smile. Fingers could be flexed to almost a complete fist and she could do all of her household work. Some pain persisted, especially at the calcinosis area over the middle joint of the fourth right finger. Deformities were still present.



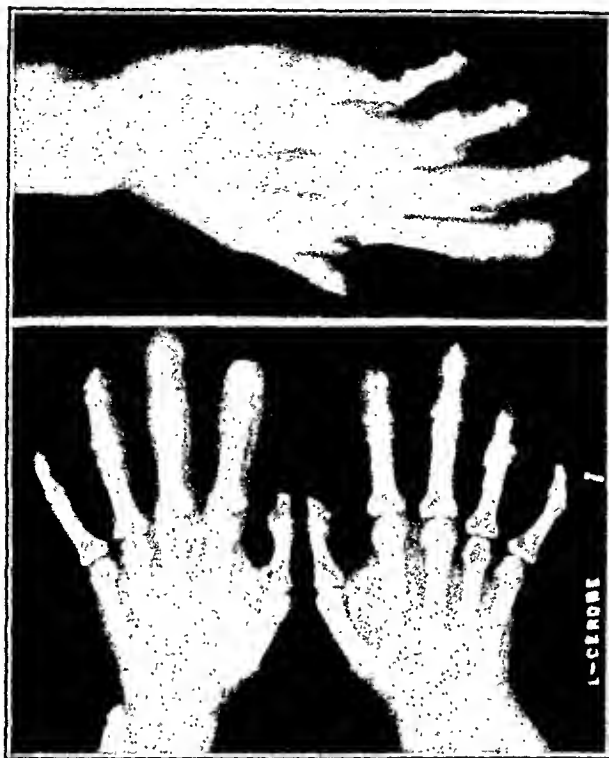


Fig. 3.—Patient L. C., x-ray films of the right hand showing atrophy of the terminal phalanges and calcinosis of the middle metacarpal joint of the fourth finger.



Fig. 4.—Patient L. C., masklike expression of the face due to the thickened skin.

**PATIENT C. D.—Present Illness:** The patient, aged fifteen years, American born of Italian parents, was first seen on May 12, 1936. She was transferred from another hospital where she had been treated for a hyperchromic anemia with accompanying symptoms of weakness and exhaustion. Fifteen months before she was seen by our clinic there developed stiffness of the skin of the hands, arms, and neck. Arsenic was found in excess in the urine and following sodium thiosulfate, 0.5 gm. three times a day by mouth, there was a marked improvement in the blood count.



Fig. 5.

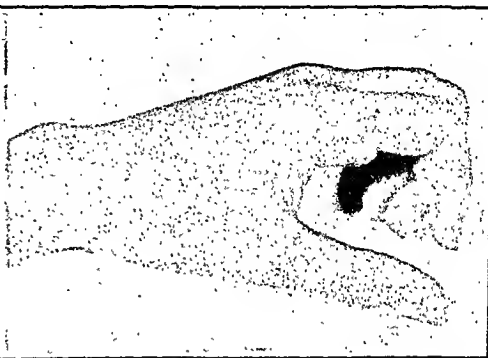


Fig. 6.

Fig. 5.—Patient C. D., maximum flexion of fingers before treatment.

Fig. 6.—Patient C. D., maximum flexion of fingers after 128 treatments with mecholyl iontophoresis.



Fig. 7.—Patient C. D., Note the pinched expression and the waxy character of the facial skin.

It rose from 2.3 millions on Oct. 27, 1935 to 5.1 millions on Dec. 17, 1935. The sclerodermal changes however increased until, when she was seen in our clinic, they were incapacitating. She could not hold anything with her hands and was unable to dress herself. Cold aggravated her symptoms and induced cyanosis.

**Past History.**—Essentially normal.

**Physical Examination.**—The patient was a fairly well-nourished and mentally alert girl of fifteen years of age. The blood pressure was 110/80; pulse, 72; all

other findings likewise normal except for thickened leathery skin over the face, neck, and hands. There were trophic changes over the knuckles and tips of the fingers with a few tiny active ulcers. Fingers could be only very slightly bent.

*Capillary Microscopy.*—There were markedly dilated capillary loops with long periods of blood stasis.

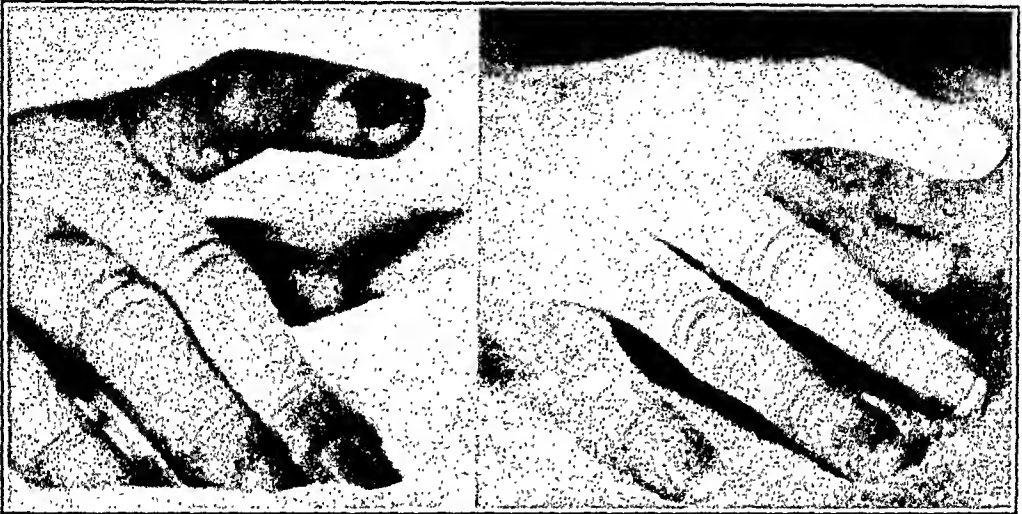


Fig. 8.

Fig. 9.

Fig. 8.—Patient H. S., ulcer on the tip of the index finger complicating scleroderma.

Fig. 9.—Patient H. S., ulcer healed after 107 treatments with mecholyl iontophoresis. Good function is present. Note the shiny skin.

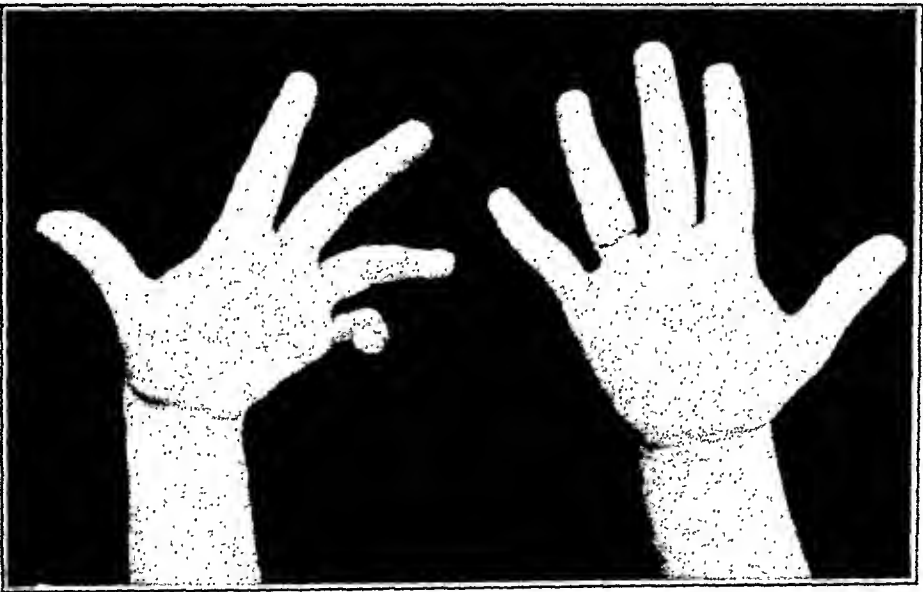


Fig. 10.—Patient M. T., scleroderma with atrophy. No Raynaud's syndrome is present. The hands show localized plaques. There was no improvement with mecholyl iontophoresis.

*Treatment.*—From May 18, 1936 until May 1, 1937 she received 128 treatments of mecholyl by iontophoresis with marked improvement. During cold weather in January, 1937 slight ulceration re-occurred over several phalangeal joints. At the termination of the treatments (May, 1937) motion was sufficient for her to carry on nearly all activities, including dressing. She could smile and open her mouth wide enough to eat easily.

We believe that the usual need of an alternate case control series is not a requisite in this study for the following reasons. First, these



Fig. 11.—Patient M. T., scleroderma with atrophy. Face deformed by a lesion on the left cheek.

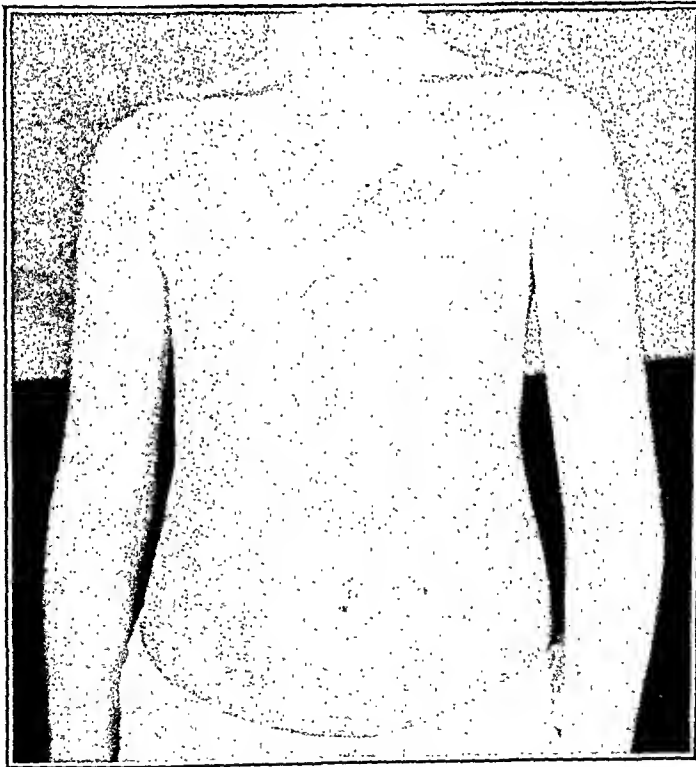


Fig. 12.—Patient M. T., scleroderma with atrophy. Isolated plaques on the chest and abdomen.

patients do not tend to have spontaneous cures and a number of them had received previous treatment of many types without results. Second, the psychic factor can be ruled out by the failure of previous elaborate

therapy, such as operative procedures. Third, previous studies with galvanism, using water or saline, failed to show improved circulation. Fourth, results from ganglionectomy are local and limited to the operated extremity, while mecholyl iontophoresis has shown softening of untreated areas.

#### COMMENT

Many of the patients in our series are still under treatment and it is likely on the basis of past experience that the list of those "markedly improved" will be somewhat larger as further treatments are given. It should be noted that the improvement is not confined to the areas treated but is observed in all areas affected by the scleroderma. There has been a tendency in several of the patients to have slight relapses; in each instance produced by some factor aggravating the Raynaud's syndrome such as cold, emotion, or trauma. It is probable that some serious relapses will occur. Several of the early treated cases have maintained their improvement without treatment. Case 1, having received eighty-five treatments, has maintained a satisfactory condition although his last therapy was given on March 18, 1936. Case 10, after 34 treatments showed marked improvement, and this has been maintained without further treatment since 1935. Many studies concerning both the disease and the treatment remain to be carried out. Blood calcium studies were done on some of the patients and for the most part showed normal figures. It is realized, however, that such figures are of very slight significance and that calcium balance studies over a long period should be undertaken in certain of these patients. Studies for arsenic in the urine were done on many of the patients. Those showing excess amounts were given a low arsenic containing diet and sodium thiosulfate intravenously without improvement. The endocrine studies were incomplete and we feel that in a careful case work-up these should be done in detail. There seems to be no connection between the use of tobacco and scleroderma, while the use of ergot may apparently aggravate the disease.

We appreciate the obvious disadvantages of this form of therapy with its technical difficulties. For the past four and one-half years we have been endeavoring without success to utilize the choline derivatives by other methods of administration.<sup>15</sup> Intravenously mecholyl is exceedingly dangerous and its effects fleeting. Subcutaneously it is also not without danger and its effects are short lived. Intranasally the risk is definitely lessened but the effects are still too brief.<sup>20</sup> Orally large and expensive doses are required. The effects are more prolonged but frequently gastrointestinal disturbances prohibit its use. Iontophoresis has advantages in that the maximum concentration of the drug may be obtained at the area most involved and that the action is prolonged over a period of four to eight hours or longer. It should not be used in any form without available atropin. The injection of  $\frac{1}{150}$  of a grain of atropin sulfate will produce a cessation of the mecholyl effects.

## CONCLUSION

A form of treatment has been presented for patients suffering from scleroderma which has given encouraging results in those receiving sufficient therapy. No other form of therapy of which we have knowledge has produced as satisfactory results. It would appear that the improvement is due to an increased vascularity in the affected parts, and a softening of the thickened dermis as a result of vasodilatation produced by acetyl beta methyl choline chloride, given by the method of iontophoresis.

Due acknowledgment is made for the technical assistance of Ellen McDevitt, B.S., and Elizabeth MacLenathen, A.B.

## REFERENCES

1. Sellei, J.: The Diagnosis and Treatment of Scleroderma and Acrosclerosis and Some of Their Kindred Diseases, *Brit. J. Dermat.* 46: 12, 253, 1934.
2. Brown, G. E., O'Leary, P. A., and Adson, A. W.: Diagnostic and Physiologic Studies in Certain Forms of Scleroderma, *Ann. Int. Med.* 4: 531, 1930.
3. Adson, A. W., O'Leary, P. A., and Brown, G. E.: Surgical Treatment of Vasospastic Types of Scleroderma by Resection of Sympathetic Ganglia and Trunks, *Ann. Int. Med.* 4: 555, 1930.
4. Ormsby, O. S.: Scleroderma Beginning With Raynaud's Symptoms, *J. Cutan. Dis. incl. Syph. N. Y.* 33: 392, 1915.
5. Devoto, A.: Case of Scleroderma Affecting Fingers; Improvement Under Polyglandular Treatment, Especially Supra-Renal Treatment, *Gior. ital. di dermat. e sif.* 66: 1071, 1925.
6. Herzog, F.: Treatment of Scleroderma by Intravenous Injections of Sodium Chloride Solution, *Med. Klin.* 22: 1178, 1926.
7. Oliver, E. L., and Lerman, J.: Therapy Injections of Posterior Pituitary Extract, *Arch. Dermat. & Syph.* 24: 469, 1936.
8. Rittenbrück, H.: Therapy—Acetylcholine, *Munchen. med. Wehnsch.* 81: 911, 1934.
9. Leriche, R., and Jung, A.: Essay on Treatment of Scleroderma by Parathyroidectomy, *Bull. et mém. Soc. nat. de chir.* 57: 609, 1931.
10. Leriche, R., and Jung, A.: Late Results of Different Parathyroid Operations in Three Cases of Scleroderma, *Rev. de chir., Paris* 73: 77, 1935.
11. Bernheim, A. R., and Garlock, J. H.: Parathyroidectomy for Raynaud's Disease and Scleroderma: Preliminary Report, *Ann. Surg.* 101: 979, 1935.
12. Osler, W.: On Diffuse Scleroderma With Special Reference to Diagnosis and to the Use of Thyroid Gland Extract, *J. Cutan. & Genito-Urin. Dis N. Y.* 16: 49, 1898.
13. Lewis, T., and Landis, E. M.: Further Observations Upon a Variety of Raynaud's Disease; With Special Reference to Arteriolar Defects and to Scleroderma, *AM. HEART J.* 15: 329, 1929-1931.
14. Prinzmetal, M.: Studies of the Mechanism of Circulatory Insufficiency in Raynaud's Disease in Association With Sclerodactylia, *Arch. Int. Med.* 58: 309, 1936.
15. Kovacs, J., Saylor, L. L., and Wright, I. S.: The Pharmacological and Therapeutic Effects of Certain Choline Compounds, *AM. HEART J.* 11: 53, 1936.
16. Kovacs, J.: The Iontophoresis of Acetyl-B-Methylcholine Chloride in the Treatment of Chronic Arthritis and Peripheral Vascular Disease: Preliminary Report, *Am. J. M. Sc.* 188: 32, 1934.
17. Saylor, L. L., Kovacs, J., Duryee, A. W., and Wright, I. S.: The Treatment of Chronic Varicose Ulcers by Means of Acetyl Beta Methylcholine Chloride Iontophoresis, *J. A. M. A.* 107: 114, 1936.
18. Barlow, G. B.: Case Report. (To be published.)
19. Moench, L. M.: A Case of Chronic Arsenic Poisoning in a Child Associated With Profound Anemia and Scleroderma, *New York State J. Med.* 36: 1029, 1936.
20. Van Dellen, T. R., Bruger, M., and Wright, I. S.: The Absorption of Acetyl-B-Methylcholine Chloride (Mecholyl) by the Nasal Mucous Membrane, *J. Pharmacol. & Exper. Therap.* 59: 4, 1937.

## FAINTING ATTACKS RESULTING FROM HYPERSENSITIVE CAROTID SINUS REFLEXES\*†

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THERE is hardly a condition in the field of medicine that disturbs a patient or affects his general morale as much as does the loss of consciousness or a severe attack of vertigo. Loss of consciousness, which is the result of various causes, is a relatively common occurrence. In the past it has been the custom to diagnose a large portion of attacks of unconsciousness as atypical forms of idiopathic epilepsy or simply to

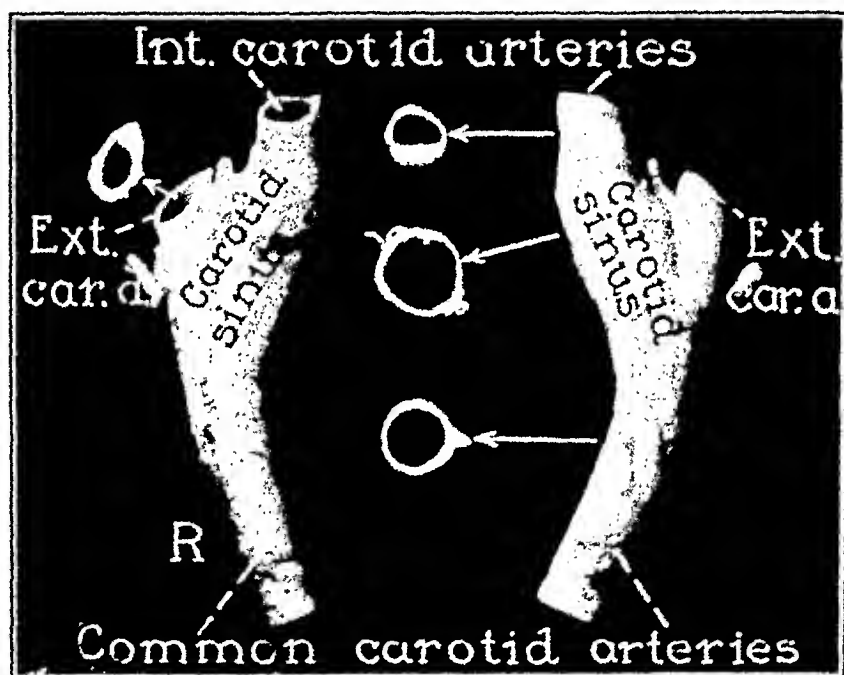


Fig. 1.—Anterior and posterior views of the right common carotid artery at its bifurcation into the external and internal carotid arteries; the carotid sinus appears in the first portion of the internal carotid artery as a bulbous dilatation.

group them under the general heading of "unconscious attacks." Just a few years ago unconscious spells due to hyperinsulinism were grouped under this general heading. Now, there is sufficient knowledge of another type of unconscious attacks to permit it to be classified as a definite clinical syndrome and to be separated from the general "unconscious attacks." This syndrome is characterized by spontaneous attacks of unconsciousness and vertigo and may or may not be associated with

\*From The Section on Cardiology, The Mayo Clinic.

†Read before the meeting of the American Heart Association, Section on Cardiac Disorders, at Atlantic City, N. J., June 8, 1937.

mild convulsions due to hypersensitive carotid sinus reflexes. The attacks may be induced by making graded pressure over one of the carotid sinuses.

#### ANATOMY OF THE CAROTID SINUS

In man and in many animals the carotid sinus is a bulbous dilatation of the first portion of the internal carotid artery<sup>1</sup> (Fig. 1). The wall

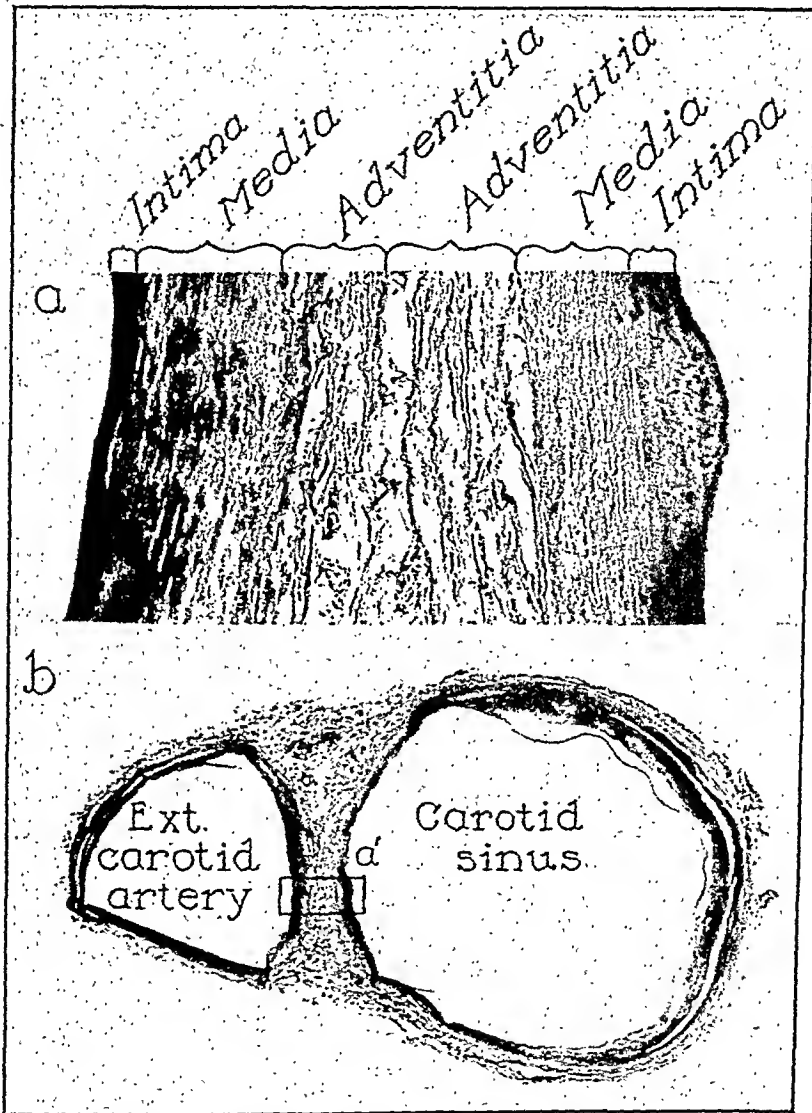


Fig. 2.—*a*, Section taken *a'* in *b*, showing wall of external carotid artery and wall of the carotid sinus; the media of the wall of the external carotid artery is thicker than the media of the wall of the sinus; the adventitia of the sinus appears thicker than that of the external carotid artery; stained with hematoxylin and eosin ( $\times 75$ ); *b*, section through the external carotid and the carotid sinus of a white woman aged fifty-five years; the carotid sinus is much larger than the external carotid artery at the same level; stained with hematoxylin and eosin ( $\times 7$ ).

of the carotid sinus is somewhat thinner than the wall of other portions of the artery. In the sinus the intima is practically the same as the intima of the rest of the artery.<sup>2</sup> The media of the sinus is thinner and contains more elastic tissue and less muscular tissue than the media of the rest of the artery (Fig. 2). The adventitia of the sinus is thicker



than the adventitia of the rest of the artery and contains special nerve cells called nerve receptors.<sup>3</sup> These nerve receptors are situated between the layers of collagen.

*Innervation.*—Investigators are not entirely agreed as to the complete innervation of the carotid sinus,<sup>2, 4</sup> but most of the outstanding investigators agree that the carotid sinus is supplied with branches from the glossopharyngeal, vagus, and cervical sympathetic nerves and occasionally by a few branches from the hypoglossal nerve. The branch from the glossopharyngeal nerve is called the nerve of Hering.<sup>5</sup>

#### THE FUNCTION OF THE CAROTID SINUS

It has been proved by physiologists that mechanical or electric stimulation of the carotid sinus produces a combined reflex or cardiac inhibition and a fall in the systolic blood pressure, that is, the same effect that is produced by stimulating the central end of a depressor nerve.<sup>6</sup> It is believed that one of the functions of the carotid sinus reflex is concerned with the control of blood pressure, the heart rate, and the maintenance of an adequate circulation in the brain. It is thought by some investigators that an increase in pressure within the sinus will, by means of a reflex, cause a drop in blood pressure and a retardation of the cardiac rate and that a decrease in pressure within the sinus will increase the blood pressure, accelerate the cardiac rate, increase respirations, and increase the secretion of epinephrine.

I do not believe that all of the functions of the carotid sinus are fully known. There is not a satisfactory explanation as to why carotid sinuses in some instances become hypersensitive, but there is no doubt that they do.

#### ELECTROCARDIOGRAMS IN THE INDUCED ATTACKS

Stimulation of a sensitive carotid sinus induces striking changes in the cardiac conduction system.<sup>7</sup> The more important changes are sudden slowing of the heart rate, varying degrees of heart-block, and long periods of complete cardiac standstill (Fig. 3). In about half of the cases observed at the clinic the cardiac slowing was sufficient to cause the fainting attacks; in the other cases the slowing was absent or too slight to be of any significance.

#### RESPIRATIONS IN THE INDUCED ATTACKS

Stimulation of a sensitive carotid sinus by mechanical pressure produces rather marked changes in respiration. In the severe attacks the breathing becomes deep and labored (Fig. 4). There did not appear to be a constant correlation between the labored breathing and the cardiac slowing and the fainting attacks.

## SYMPTOMS AND DIAGNOSIS

Carotid sinus syncope is much more common among males than among females. In the series of eighty-five cases observed at the clinic the ratio of males to females was 5:1. It is most common among middle-aged persons and elderly individuals and is rare among young persons. In this series of cases the oldest patient was seventy-eight and the young-



Fig. 3.—Electrocardiogram (Lead II) for a man aged fifty-nine years: A, B, C, D, E, and F represent continuous tracing; first arrow indicates beginning of pressure on the right carotid sinus; subsequently, cardiac standstill of 6.6 sec. with development of a convulsion at third arrow; idioventricular rhythm shown between first and last arrows.

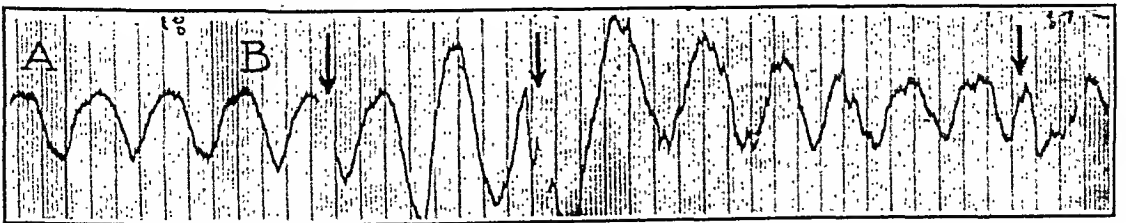


Fig. 4.—Respiratory response to carotid pressure in a man aged sixty-four years: A to B represents normal respirations; first arrow indicates pressure on the right carotid sinus; respirations became slower and deeper and patient became unconscious at second arrow and regained consciousness at third arrow.

est was twenty-eight years of age. The average age of the patients was fifty-six years. The chief symptoms were attacks of vertigo and spells of unconsciousness; mild convulsions may be associated with the syncopal attacks. A definite aura is usually present; this consists of weakness, lightheadedness, spots before the eyes, and epigastric distress. Patients often turn pale, perspire profusely, and complain of sensation

of numbness in the extremities. During the unconscious attacks the pupils usually dilate; during one of the induced attacks there was a definite exophthalmos which receded quickly at the termination of the attack. The vertigo usually comes on in the attacks, the patient being usually free from dizziness between the attacks. During the attacks of vertigo patients often stagger and occasionally fall. The attacks of unconsciousness usually last from a few seconds to fifteen or twenty minutes; the average attack lasts one to four minutes. The spontaneous attacks of unconsciousness practically always occur when the patient is either sitting or standing and rarely when the patient is lying down. Attacks of fainting occasionally are precipitated by changing the position of the body, turning the head to the right or left, or looking upward. Any pressure on the neck, such as tight collars or carrying sacks of grain on the shoulders, also may bring on attacks. It is common for spells to occur in barber chairs when towels are placed rather tightly around the patient's neck and when the patient changes the position of his body rather quickly. In most instances, the precipitating factors in the spontaneous attacks are unexplained.

#### BLOOD PRESSURE DURING THE ATTACKS

There has not been an adequate study of the blood pressure during spontaneous attacks. In the induced attacks the blood pressure usually decreases; this decrease varies from a slight to a severe depression of blood pressure. The fall in blood pressure was greatest in cases of hypertension. In a few instances there was a slight rise in blood pressure during the induced attacks.

In the attacks of unconsciousness the patient may have a mild or a severe convulsion. Patients practically never bite their tongues or lose control of their sphincters. The induced attacks are usually of shorter duration than the spontaneous ones. The diagnosis is made from the history and by inducing an identical attack by making graded pressure on one of the carotid sinuses. It should not be necessary to induce an attack by making pressure on both sinuses at the same time.

#### TECHNIC IN EXAMINING PATIENTS FOR HYPERSENSITIVE CAROTID SINUS

The patient should preferably be in a sitting position, with the head tipped slightly backward to one side and away from the side being examined. The sinus is usually situated just below the angle of the jaw and at the level of the upper border of the thyroid cartilage. The situation is somewhat variable, however. The carotid bulb frequently can be definitely palpated. Pressure is made with the thumb, compressing the sinus against the spinal column. The characteristic response will usually occur in ten to twenty-five seconds. This depends on the efficiency of the examiner and the sensitivity of the sinus.

## TREATMENT

In a certain portion of the cases the symptoms are mild and the attacks occur so infrequently that no treatment is required. In cases in which the attacks are moderately severe, the patients are advised to avoid turning their heads quickly, looking upward and stooping suddenly; they also should avoid any constriction on the neck, especially tight collars.

The drugs that are usually recommended are ephedrine, epinephrine, benzedrine, and atropine. In my experience, drugs have not proved particularly satisfactory.

Operation is the treatment of choice in cases in which the attacks are moderately severe or severe. The operation consists of denervation of the carotid sinus and portions of the common, external, and internal carotid arteries.

*Prognosis.*—This is not a killing disease. I do not know of a proved case in which the patient died in an attack. As far as recovery is concerned, patients may have these attacks for many years.

## REFERENCES

1. Smith, H. L., and Moersch, F. P.: Further Study on the Hypersensitive Carotid Sinus Reflex Syndrome: Report of Thirty-One Additional Cases, *Proc. Staff Meet. Mayo Clinic* 11: 380, 1936.
2. Ask-Upmark, Erik: The Carotid Sinus and the Cerebral Circulation: an Anatomical, Experimental, and Clinical Investigation Including Some Observations on Rete Mirabile Caroticum, *Acta psychiat. et neurol. Suppl.* 6, p. 39, 1935.
3. De Castro, F.: Sur la structure et l'innervation du sinus carotidien de l'homme et des mammifères. Nouveaux faits sur l'innervation et la fonction du glomus caroticum. *Univ. Madrid Trav. du Lab. de rech. biol.* 25: 331, 1928.
4. Code, C. F., and Dingle, W. T.: The Carotid Sinus Nerve, *Proc. Staff Meet. Mayo Clinic* 10: 129, 1935.
5. Hering, H. E.: Die Karotissinusreflexe auf Herz und Gefäße von normal-physiologischen, pathologisch-physiologischen und klinischen Standpunkt. Gleichzeitig über die Bedeutung der Blutdruckzügler für den normalen und abnormen Kreislauf. Dresden, 1927, Th. Steinkopff, 150 pp.
6. Starling, E. H.: *Principles of Human Physiology*, ed. 6, Philadelphia, 1933, Lea and Febiger, p. 795.
7. Weiss, Soma, and Baker, J. P.: The Carotid Sinus Reflex in Health and Disease; Its Role in Causation of Fainting and Convulsions, *Medicine* 12: 297, 1933.
8. Schmidt, C. F.: Carotid Sinus Reflexes to the Respiratory Center: I. Identification, *Am. J. Physiol.* 102: 94, 1932.

## THE USE OF QUINIDINE SULFATE INTRAVENOUSLY IN VENTRICULAR TACHYCARDIA\*

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**P**AROXYSMAL ventricular tachycardia occurs very infrequently and, with very few exceptions, appears in patients with serious structural heart disease. Its appearance is often an indication of an impending fatal termination. In these respects it differs entirely from paroxysmal auricular tachycardia which is of common occurrence, rarely appears in people with structural heart damage, and seldom turns the scale against the patient.

Of this series of 26 cases of ventricular tachycardia two are from the private records of Dr. J. A. Oille and the remaining 24 are from the wards of the Toronto General Hospital. These 24 cases occurred during the past seventeen years and show the rarity of ventricular tachycardia, as during that time electrocardiograms have been done on 12,000 patients having or suspected of having heart disease. Cardiac infarction was the diagnosis in 12 of the 26 cases, the infarction having occurred from a few hours to several weeks before the onset of ventricular tachycardia. Four were cases of degenerative heart disease. Two patients were suffering from hypertensive heart disease, one of them also having uræmia. Chronic rheumatic heart disease accounted for three cases. Too liberal administration of digitalis may have been the cause of the ventricular tachycardia in three cases, as the tachycardia was preceded by frequent extrasystoles and cleared up on stopping the digitalis. However all three died a few days later. Ventricular tachycardia appeared in a case of chronic rheumatic heart disease and in a case of hyperthyroidism, both of which were being given quinidine sulfate by mouth in an attempt to clear up auricular fibrillation. We believe that the ventricular tachycardia in these two cases was due to quinidine sulfate administration.

Definite structural heart disease was present in all the cases except the hyperthyroid case, a man of thirty-five who was being given quinidine by mouth preoperatively for auricular fibrillation. We no longer use quinidine preoperatively in cases of hyperthyroidism for two reasons: normal rhythm is likely to reappear following opera-

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Read before the American Heart Association, section on cardiac disorders, at Atlantic City, N. J., June 8, 1937.

tion, and when auricular fibrillation has been stopped preoperatively by quinidine the fibrillation frequently reappears following operation.

We have included no cases in which the paroxysms of tachycardia were of brief duration. In several of these cases the paroxysms lasted for several days continuously. Only cases of longer duration are considered because of the impossibility of evaluating the results of any form of treatment in paroxysmal attacks of any kind, particularly if the paroxysms are of short duration.

While ventricular tachycardia can often be recognized clinically, the diagnosis was made or confirmed in all our cases electrocardiographically.

It is well recognized that digitalis, mechohyl, and carotid sinus stimulation have no effect on ventricular tachycardia. The attacks either end spontaneously or are stopped by quinidine sulfate. We have tried digitalis, mechohyl, and carotid sinus stimulation on several of the cases without any results.

The onset of ventricular tachycardia is often accompanied or followed by a profound degree of shock, as evidenced by marked fall in blood pressure, cyanosis, dyspnea, nausea, vomiting, and even coma. Nine of our patients were severely shocked, while the remainder appeared to be little if at all upset by the ventricular tachycardia. Seven of the 9 cases showing marked shock had had cardiac infarction recently or fairly recently. The diagnosis in the other two cases was hypertensive heart disease with uremia in one and degenerative heart disease in the other.

The fact that a marked degree of shock accompanied ventricular tachycardia in only 9 of the 26 cases naturally raises the question as to whether the shock was due to the ventricular tachycardia or to the underlying heart condition. The immediate and invariable improvement in the shocked patients on the restoration of sinus rhythm strongly suggests that in these cases at any rate the shock was due in part at least to the abnormal rhythm.

Prior to 1931, when we began to use quinidine sulfate intravenously in cases of ventricular tachycardia, all our cases showing this rhythm died within a few days of the onset of ventricular tachycardia, with the exception of the cases in which the ventricular tachycardia was due to quinidine given to clear up auricular fibrillation.

Quinidine sulfate was used intravenously only when shock was severe and vomiting made the oral administration of the drug impossible.

*Administration.*—Quinidine sulfate is relatively insoluble in water, and we have found that it can be dissolved more readily in 5 per cent glucose or in normal saline solution. By vigorous shaking 50 to 60 grains can be dissolved in 500 c.c. of 5 per cent glucose. The solution is then filtered and given intravenously, slightly warmed, at the rate of 100 to 120 c.c. an hour. While it is being administered, blood pressure readings are taken frequently on the other arm.

We have given quinidine sulfate intravenously to 9 patients, one of them receiving a dose on three different admissions. One case, a man of thirty-six, was admitted two weeks after an attack of coronary thrombosis. On the day after admission he developed ventricular tachycardia and his blood pressure fell to 90/78. Carotid sinus stimulation was tried on both sides without effect. Intravenous quinidine sulfate was then started and after 9 grains had been given he complained of low sternal pain, became restless and more cyanosed, and his blood pressure fell to 70/?. Quinidine was discontinued and coramine given intravenously but the blood pressure continued to fall to 50/?. Fifteen grains of caffeine sodio-benzoate intravenously brought the blood pressure up to 104/76 in five minutes and his dyspnea, color, and pain improved. Next day, ventricular tachycardia still being present, digoxin and strophanthin were tried unsuccessfully and, vomiting being no longer present, he was given quinidine sulfate by mouth, 10 grains hourly for three doses. After an interval of three hours the same dose was repeated and on the following morning normal rhythm was present.

This is the only case in which quinidine sulfate intravenously seemed to have an adverse effect, but the subsequent progress of the patient has been satisfactory as he is well and at work two and a half years later.

A fairly typical case was H. N., a male aged thirty-five years, admitted July, 1935, with the following history. On the day before admission he had severe epigastric oppression with heart pounding and several syncopeal attacks and vomiting. He was admitted to hospital deeply unconscious, with Cheyne-Stokes respirations and cyanosis and appeared to be moribund; blood pressure 60/0; heart rate 230. Electrocardiogram showed ventricular tachycardia. By the time intravenous quinidine sulfate was started his heart rate was 250; in twenty minutes his heart rate was 160 and blood pressure 94/60; in one hour the rate was 140 and blood pressure 100/70; in one hour and thirty-five minutes the rate was 72 and blood pressure 114/80. He received 17 grains of quinidine sulfate and was conscious and comfortable before the intravenous injection was discontinued. A few days later ventricular tachycardia reappeared, with a heart rate of 250, but without vomiting. He was given two doses of 15 grains of quinidine sulfate by mouth and during the ensuing three hours his heart rate fell: 250—200—160—80. Electrocardiograms showed changes typical of coronary thrombosis. After six weeks in bed and a few weeks convalescing he returned to his former work and was still well in June, 1937.

This case was exceptional in that the heart rate was much faster than in the others in which it usually ran from 160 to 180 per minute.

The average amount of quinidine administered to the patients in this series was slightly less than 20 grains. One patient received 35 grains.

Of the 9 patients treated intravenously since 1931 three are dead, one succumbing to another attack of coronary thrombosis two weeks after the ventricular tachycardia. Another had hypertensive heart disease and the ventricular tachycardia had been present for two days before quinidine was used. After 20 grains intravenously, ventricular tachycardia stopped but the patient died of uremia a week later. The third fatal case was that of a man who since 1931 had six admissions to the hospital for attacks of coronary thrombosis. On five of the admissions ventricular tachycardia was present. On three occasions he seemed moribund, was pulseless, and received quinidine sulfate intravenously. On two occasions the ventricular tachycardia was not accompanied by severe shock and quinidine sulfate was given by mouth. He died in December, 1935, and the autopsy showed extensive sclerosis of the coronary arteries, the left anterior descending branch being a double vessel with recanalized thrombi and recent thrombi, and old and recent infarcts of the apex of the left ventricle and adjoining septum. The remaining six patients are alive.

The fate of the 17 cases of ventricular tachycardia not receiving quinidine sulfate intravenously is of interest. Three are alive, the other 14 having died within fifteen days of the onset of ventricular tachycardia. Of the 3 who survived, two were the cases in which ventricular tachycardia was believed to be due to quinidine sulfate therapy for auricular fibrillation. The third was a case of coronary thrombosis. Ventricular tachycardia appeared twenty-six days after the coronary thrombosis and was accompanied by a slight fall in blood pressure. The ventricular tachycardia disappeared after one dose of quinidine sulfate by mouth.

#### SUMMARY

Ventricular tachycardia is at times accompanied by shock of such severe degree that the patient appears to be moribund. This state of shock is due, in part at least, to the ventricular tachycardia, as improvement is marked when normal rhythm is restored.

We recognize the difficulty of evaluating the treatment of any paroxysmal affection, but when six out of 9 cases treated intravenously are alive for periods up to four years, and only one of the remaining 17 cases lived longer than fifteen days (omitting the two cases due to quinidine administration), we feel that the administration of quinidine sulfate intravenously may be life-saving.

We suggest that the intravenous administration of quinidine sulfate be restricted to cases of ventricular tachycardia in which shock and vomiting preclude the oral administration of quinidine sulfate.



# Department of Reviews and Abstracts

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## Selected Abstracts

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Lendle, L.: The Factors Involved in the Action of K-Strophanthidin (Distribution, Elimination and Cumulation) and the Effectiveness of Several Strophanthidin-Ester Combinations. *Arch. f. exper. Path. u. Pharmacol.* 182: 72, 1936.

Ester combinations of K-strophanthidin were as effective on the frog as the genin but only one-half to one-third as effective as the glucoside. Even the most active ester combination (isovaleryl ester) is less effective than K-strophanthin in warm-blooded animals. The lethal dose given of the genin subcutaneously is five times the doses used intravenously, whereas in the case of the glucoside, the subcutaneous lethal doses are only twice the intravenous. It was found that 12.3 per cent of the fatal dose of the glucoside is excreted per hour while 25 per cent of the fatal dose of the genin is excreted per hour. One-tenth of the total fatal dose of glucoside is bound by the heart, the genin is apparently bound in the same proportions.

The smallest cumulating dose of the genin is 15 to 20 per cent of the fatal dose whereas for the glucoside, it is 7 to 10 per cent.

These studies indicate that the difference between glucoside and genin is only a quantitative one.

L. N. K.

Dieckhoff, J.: Power of the Heart With and Without Hypertrophy With Aortic Insufficiency as Determined in the Heart-Lung Preparation. (The Action of Digitalis on Such Preparations.) *Arch. f. exper. Path. u. Pharmacol.* 182: 268, 1936.

The production of aortic insufficiency in the cat heart causes a decreased duration as compared to the normal heart of the viability of the heart when used under strain in the heart-lung preparation. The power of the aortic insufficiency heart is decreased also. This effect is found during the first sixty days following aortic insufficiency. Hearts having this lesion for one hundred to one hundred and fifty-four days and showing marked hypertrophy approach the normal power in the heart-lung preparation. The use of an artificial valve to prevent an aortic leak restored the nonhypertrophied heart to normal power. In the hypertrophied heart the artificial valve makes the heart more efficient than normal. Preliminary digitalization of the heart with aortic insufficiency makes it more powerful.

L. N. K.

Straub, W., and Scholz, J.: Studies on the "Vagus Substance." *Arch. f. exper. Path. u. Pharmacol.* 182: 331, 1936.

A new method of studying humeral transmission of vagus action is described. The inhibition of esterase by physostigmin and prostigmin is demonstrated. Hydrocyanic acid has a similar action. All three substances, therefore, enhance the effect.

L. N. K.

Friedrich, L. V.: Is Heart Action Influenced by the Gastro-Intestinal Tract? Arch. f. Verdauungskr. 60: 67, 1936.

In cases of patients with either normal or diseased hearts, distention of the gastrointestinal tract with air or other gases has no influence on the heart rate or the blood pressure, except when the diaphragm is elevated. Under the latter circumstance, pain may occur.

L. N. K.

Zaeper, G.: Measurement of Pulmonary Blood Flow. Beitr. z. Klin. d. Tuberk. 88: 79, 1936.

A method is presented for clinical use based on the Fick principle. Alveolar air and saturation of the blood are used in calculating the A-V  $O_2$  difference. This and the  $O_2$  consumption per minute is the basis of flow determination. Four trained individuals had a minute volume flow of 20.8 liters on the average. Five untrained individuals had a minute volume flow of 28.2 liters.

L. N. K.

Lucadou, W. v.: The Adrenals in Chronic Heart Involvement. Beitr. z. path. Anat. u. z. allg. Path. 96: 561, 1936.

The medulla of the adrenal is hypertrophied in chronic cardiac patients whether renal or essential hypertension is present or not. In patients with chronic nephritis and hypertension, an increase is shown in the size of the adrenal cortex as compared to those without these complications.

L. N. K.

Pfuhl, W.: The Manner in Which Heart Action Is Assisted by Intrathoracic Suction. Deutsches Arch. f. klin. Med. 179: 247, 1936.

The filling of the heart is aided by an elastic pull of the lungs. This is equivalent to a pull of 3 to 5 kilograms during normal breathing. It acts on the auricles during ventricular systole, on the ventricles during auricular systole and on the whole heart during diastole. Part of ventricular systole is used to augment this lung suction power.

L. N. K.

Gurewitsch, J. B.: Variability of Heart Size. An Investigation of 193 Pairs of Twins. Fortschr. a. d. Geb. d. Röntgenstrahlen 54: 62, 1936.

The ages of the twins studied were from four to eleven years. It was found that size, weight, and chest diameter have an equal effect on heart size, but their effect is not great. Previous disease (one and one-half to two years before examination) such as scarlet, diphtheria, and typhus have no effect.

L. N. K.

Seekles, L.: Action of Magnesium on the Heart. Klin. Wchnschr. 15: 1434, 1936.

Tachycardia, block, and standstill occur following the intravenous use of calcium chloride in veterinary fields. The use of magnesium chloride in the proper dose avoids the danger of block and standstill, the ratio being 4 parts of calcium to 1.5 of magnesium.

L. N. K.

Aschenbrenner, R.: The Digitalis Electrocardiogram. *Klin. Wchnschr.* 15: 1039, 1936.

The depression of the S-T segment following digitalis is attributed to a slowing of ventricular conduction. Strophanthin as distinguished from other digitalis preparations does not change the S-T segment; this is thought to indicate a less marked effect on conduction by this drug.

L. N. K.

Schwingel, E.: Value of the Initial Complex of the Electrocardiogram as a Test of Heart Function. *Ztschr. f. d. ges. exper. Med.* 98: 539, 1936.

In normal persons exercise causes a decrease in QRS duration. In patients with heart disease QRS duration is increased with exercise.

L. N. K.

de Châtel, A.: The Abnormal Deviations of the Final Complex of the Electrocardiogram in Local Leads, III. *Ztschr. f. d. ges. exper. Med.* 99: 207, 1936.

The effect of cardiac dilatation on the T-wave was determined. The dilatation was produced in the dog by compression of the aorta or the pulmonary artery. Dilatation of the right ventricle makes the T negative and dilatation of the left ventricle makes the T taller. Local (unipolar) leads show that this is due to earlier deactivation of the dilated chamber.

L. N. K.

Schlomka, G., and Reindell, H.: Concerning the Clinical Electrocardiography. V. The Changes in the Curve With Shift From the Reclining Position to Standing. *Ztschr. f. klin. Med.* 130: 313, 1936.

The authors found that not only does the pulse accelerate on standing up, but QRS becomes smaller and T becomes notched or diphasic. At times, the electrocardiogram may resemble that in coronary occlusion when the subject stands up. These are reversible changes, reaching a maximum in 8 to 15 seconds and usually receding after a few minutes. Despite acceleration of the heart, systole may not shorten in duration. Changes are due in part to a lack of blood supply to the heart, following redistribution of blood on standing up and in part to stimulation of pressor nerve receptors. The degree of change in the electrocardiogram is a function of the state of the heart and the electrocardiographic changes on standing up may be used as a functional test of the heart. Its importance in aviation is emphasized.

L. N. K.

Faleiro, A.: Electrocardiographic Diagnosis of Ventricular Hypertrophy. I. Left Ventricular Hypertrophy. *Ztschr. f. klin. Med.* 131: 147, 1936.

The author determined the potential quotient (Groedel's method) from the ratio of the major upward deflection of QRS in a precordial lead over the left parasternal line and that in the precordial lead over the left midaxillary line at the level of the xyphoid. This ratio was never more than 2.3 in males and 2.6 in females with normal hearts (250 cases) or heart disease without hypertrophy (140 cases). In left ventricular hypertrophy 80 per cent of the (41) cases had values over 2.5 in males and 3.0 in females. Cases with right ventricular hypertrophy (10) had values less than 0.8. This method, according to the author, is thus of value in determining hypertrophy.

L. N. K.

Faleiro, A.: The Localization and Prognosis of Anterior Wall Infarction With the Aid of the Electrocardiogram. *Ztschr. f. klin. Med.* 130: 808, 1936.

The author reports 50 cases of anterior wall infarction and 30 of posterior wall infarction. The precordial lead from the apex showed a mainly or entirely inverted initial deflection in 20 of the anterior infarcts and in all cases of posterior infarction. In the rest of the anterior infarcts the QRS was positive with or without an initial negative phase. In 12 of these an apical infarct was demonstrated postmortem. In 80 instances without infarction, the QRS was inverted except in 5 cases of right ventricular hypertrophy in which the QRS was upright. In 29 cases of apical infarct precordial leads from the fourth intercostal space to the left of sternum, 27 showed an absence of the initial phase of QRS; in the others it was small.

L. N. K.

Riseman, Joseph E. F., and Brown, Morton G.: Medicinal Treatment of Angina Pectoris. *Arch. Int. Med.* 60: 100, 1937.

The use of fifteen different drugs in the treatment of twenty-six patients with angina pectoris was studied. Each drug was given several times a day for at least a week before its effect was evaluated. The efficacy of treatment was ascertained by the usual clinical methods and also by determining how much work, under standardized conditions, the patient could perform before pain developed. Control observations were made to differentiate between spontaneous remissions and improvement due to treatment.

The patient's estimation of therapeutic benefit indicated that all the drugs were approximately equal in value. Placebos were just as often beneficial as other medicaments.

The exercise tolerance test revealed that patients whose treatment consisted of lactose, sodium bicarbonate, potassium iodide, or tissue extract were unable to perform any more work than was possible without medication.

Glyceryl trinitrate given before work was undertaken prevented attacks and enabled many patients to do considerably more work. This prophylactic effect was often of relatively short duration, but attacks were prevented for as long as an hour in many cases. Such patients could be rendered completely free from attacks in daily life by taking glyceryl trinitrate at hourly intervals. For all practical purposes small doses ( $\frac{1}{500}$  grain, or 0.1 mg.) were as valuable as larger doses and were attended by little discomfort.

One-half of the patients were benefited by either aminophylline or quinidine sulfate. Aminophylline had to be given in doses of 3 grains (0.2 gm.) to be effective.

Theophylline calcium salicylate, erythrol tetranitrate, and atropine sulfate were often of value; occasionally they benefited patients not helped by either aminophylline or quinidine sulfate. The doses of atropine necessary frequently caused discomfort because of side reactions.

Codeine sulfate and phenobarbital rarely enabled the patient to do more work before pain developed, but these sedatives appeared to be of aid as an adjunct in the treatment of the patient.

Sodium nitrite and small doses of dinitrophenol were only rarely of benefit. Other more effective drugs are available, and dinitrophenol, even in the small doses used, occasionally gave undesirable side reactions.

Digitalis was rarely of value and frequently caused a striking increase in anginal attacks.

AUTHOR.

Battro, A., and Braun Menendez, E.: *Electrocardiographic Studies of Mitral Stenosis*. *Rev. argent. de cardiol.* 4: 1, 1937.

Simultaneous records of venous pulse, heart sounds, and electrocardiogram in 15 cases of mitral stenosis allowed the following conclusions:

The diastolic murmur, in cases of sinus rhythm, is definitely reinforced, during the rapid ventricular inflow and during auricular systole; in cases of auricular fibrillation the second reinforcement (presystolic murmur) is lacking, and the diastolic is so brief that it may simulate a sound. If the heart action is rapid, it occupies the whole diastole, and gets so close to the first heart sound that it may be clinically taken as a presystolic murmur. In cases of sinus rhythm the presystolic murmur may be absent in the event of a prolonged diastole. In all cases its "in-crescendo" character is inconstant.

The first heart sound often shows murmuric vibrations during the isometric contraction phase. They may be interpreted as a slight degree of mitral insufficiency. In cases with auricular fibrillation, especially after prolonged diastolic pauses, the first heart sound begins with a slow wave which practically coincides with the initiation of the QRS complex.

A three-sound rhythm frequently results from reduplicated second sounds or opening snap of the mitral valve. The former is more easily recognized at the base, whereas the latter is more easily found over the noncovered and apex regions, although they may be recorded from other areas and even simultaneously coexist. For the correct interpretation of the phonocardiograms the venous pulse record is necessary to furnish adequate reference points.

Even though a reduplication of the second sound was not systematically sought for, it was recorded in 5 cases. The opening snap was found in 7; in two of them it was clearly separated from the diastolic murmur by a short interval and in the remaining 5 the vibrations of the murmur immediately followed it, the snap being only recognizable by the higher amplitude and lower frequency of its vibrations. In the 8 remaining cases the beginning of the diastolic murmur coincided with the top of the wave of the venous pulse without any clear difference between the initial and consecutive vibrations.

AUTHOR.

Wilson, May G., and Schweitzer, Morton D.: *Rheumatic Fever as a Familial Disease. Environment, Communicability, and Heredity in Their Relation to the Observed Familial Incidence of the Disease*. *J. Clin. Investigation* 16: 555, 1937.

There is presented a consideration of the rôle of environment, contagion, and heredity as factors responsible for the familial incidence of rheumatic fever in 112 families, observed over a period ranging from three to eighteen years.

There did not appear to be a direct relation between the environments studied and the incidence of rheumatic fever. One-third of the 112 families lived under relatively favorable environmental conditions. In the former group the incidence of rheumatic siblings was 53 per cent, as compared with 46 per cent in the latter group.

There was no direct relation between the type and source of exposure and the resulting activity. The incidence of rheumatic fever following "active exposure," and "inactive exposure" was comparable. Intimate contact ("familial exposure") and casual contact ("extra-familial exposure") were equally effective.

Only 21 per cent of 968 person years of active exposure could be related to subsequent rheumatic activity.

In a total of 55 families with rheumatic parents, in 47 per cent, activity followed active exposure; in 53 per cent, activity followed inactive exposure.

In 57 families with nonrheumatic parents, in 57 per cent, activity followed extra-familial exposure (casual contact); in 43 per cent, activity followed familial exposure (intimate contact).

The interval between active or inactive exposure and the onset of rheumatism was one year in 20 per cent; two to five years in 49 per cent; and six to eleven years in 31 per cent.

The 227 rheumatic siblings experienced 588 calendar years of rheumatic activity. Of these years, 159, or 27 per cent, were simultaneous years of rheumatic activity.

The interval between the related manifestations was: One month, 29 per cent; one to two months, 24 per cent; two to eleven months, 47 per cent. Three-fourths of the related manifestations of rheumatic activity were between joint pains and other rheumatic manifestations. One-fourth of the related manifestations was between polyarthritides, carditis, and chorea. In 66 per cent the interval between these major manifestations was two to eleven months.

In 51 families, 59 parents (mother or father) were rheumatic; 44 per cent experienced rheumatic activity during the lifetime of the siblings. In no instance did a negative parent acquire the disease. The incidence of rheumatic siblings was comparable in families with a rheumatic mother or father.

Of 112 rheumatic families, 49 per cent had parental rheumatism. In only 28 per cent of the families were parents and pedigree on maternal and paternal sides apparently negative.

Of a total of 468 siblings over the age of three years, 48 per cent were rheumatic; 46 per cent males and 54 per cent females.

All identical twins cited (4 pairs) were alike in having rheumatic fever. Of the 12 pairs of fraternal twins, 5 pairs had similar incidence, i.e., both positive or both negative, and 7 pairs had dissimilar incidence.

A genetic analysis of the data corrected for size of family gave agreement between observed and expected values.

For children of 58 pairs of negative parents, the observed incidence was 94, the expected value 88.

For children of 37 positive mothers, the observed incidence was 90, the expected value 86.

For children of 29 positive fathers, the observed and expected incidences were respectively 29 and 27.9.

The hereditary mechanism involved was a single autosomal recessive gene. Dominance, involving one or more genes, and recessives involving two or more genes, as well as sex linkage were all excluded.

AUTHOR.

Palmer, J. H.: The Blood Pressure in the Years Following Recovery From Coronary Thrombosis. *Lancet* 1: 741, 1937.

An analysis was made of the blood pressure findings in 212 patients who survived an attack of coronary thrombosis by at least three months. The incidence of hypertension (160 mm. systolic and/or 100 mm. diastolic) as determined by readings made before or at any time after the attack, was found to be 73 per cent. More than half the cases showed hypertension during the first year. The hypertensive group included 37 per cent of those aged under fifty, and 78 to 84 per cent of those in the next three decades of life at the time of the attack. All except one of the 20 female patients were hypertensives.

The average course of the blood pressure during ten years after coronary thrombosis (not including the first month following the attack) has been plotted. The systolic pressure showed a slight rise during this period while the diastolic showed a slight fall.

Evidence is adduced to show that the average blood pressure for the series before the attack was probably about 170/100. Although on the average the prior levels were not regained during the ten-year period, they were in a few cases actually exceeded.

AUTHOR.

Kalbfleisch, H.: Phrenico-Pleural Collateral Circulation. *Frankfurt. Ztschr. f. Path.* 49: 10, 1936.

A case of embolic-thrombotic closure of the left lower pulmonary artery in a fifty-two-year-old cardiac patient is described in which the blood supply came from collaterals from the diaphragm to which the lung had become adherent. The left bronchial artery was also found to be dilated.

A second case of Laennec cirrhosis of the liver, liver carcinoma, congestion of the systemic and pulmonary circuits in a fifty-five-year-old man is reported in which venous collaterals had been established between the portal vein, veins in the abdominal wall, and veins in the right side of the diaphragm. In addition venous collaterals were present between the diaphragm and the pulmonary veins of the adherent lung.

L. N. K.

Linton, Robert K.: Acute Peripheral Arterial Occlusion and Its Treatment. *New England J. Med.* 216: 871, 1937.

In general, there are four types of treatment of embolism: (1) Embolectomy, (2) the use of intermittent negative and positive pressure, (3) the use of vasodilators, and (4) symptomatic or "watchful waiting." Embolectomy was successful in 4 out of 9 cases. Careful localization was made preoperatively, by means of palpation and the use of an aneroid sphygmomanometer. Negative-positive and negative pressure treatment was successful in 9 out of 12 cases. This is especially encouraging in that these cases were not suitable for embolectomy because of the poor condition of the patients. The average length of treatment necessary to establish an adequate circulation was four and one-half days. One of the patients treated successfully by means of negative-positive pressure had a large embolus occluding the bifurcation of the aorta and the arteries below the bifurcation. The author believes that early application of intermittent negative-positive pressures prevented formation of secondary thrombi in the arteries distal to the occlusion. The author has no data on the use of vasodilators, since he did not wish to complicate the results of the other methods of treatment. In only one of 13 cases receiving no treatment was the limb saved. Of 5 cases of embolus in the arm, 4 recovered with no treatment but these cases were not included because of the frequency of spontaneous development of collateral circulation in this extremity.

The best results from a single method of treatment of embolus was suction and pressure therapy. The writer believes the ideal method of treatment for suitable cases is a combination of treatments, namely, embolectomy followed by use of the suction-pressure treatment and also the production of peripheral vasodilatation. In cases properly treated, a still higher percentage of extremities should be saved.

H. M.

Pick, E. P.: Automatic Adjustment and Regulation of the Circulation. Presented at the International Medical Week in Lucerne, Sept. 1, 1936. Taken from an abstract in the *Ztschr. f. Kreislaufforsch.* 29: 226, 1937.

In addition to nervous and neurohumoral regulation of cardiac activity, there is an important group of physical regulatory mechanisms; viz., diastolic, filling and distention of the heart, venous return, coronary flow, and pericardial restraint. The action of blood reservoirs in regulating blood volume and avoiding congestion is established, the liver being important in this connection. A number of metabolic products such as  $\text{CO}_2$ , lactic acid, histamine, and acetylcholine, adenylyphosphoric acid are important in regulating the circulation. These and the hormones and vitamins form a second important mechanism. They operate not only directly on the circulating system but reflexly. A third mechanism is the blood pressure regulators, the end organs which tend to keep the blood pressure constant. These various stimuli summate (or neutralize each other) so that the circulation is well adjusted to its requirements.

L. N. K.

Heier, H.: Changes in the Wall of the Heart in the Roentgenkymogram. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 53: 895, 1936.

In one case diagnosis of aneurysm at the apex of the heart due to infarction was diagnosed with certainty only by the kymograph. It is valuable also in other types of myocardial damage and in pericardial adhesions. Changes in the amplitude of pulsations indicate myocardial disease; persistence of pulsations with a change in heart contour indicate extracardiac processes.

L. N. K.

Brenner, F., and Wachner, G.: Unusual Location of Cardiac Aneurysm and Its X-ray Diagnosis. *Fortschr. a. d. Geb. d. Röntgenstrahlen* 54: 243, 1936.

A calcified bulge of the heart in the region of left pulmonary hilus was noted in the roentgenogram in a sixty-four-year-old subject. At autopsy this proved to be an old aneurysm of the posterior wall of the base of the left ventricle. It was associated with closure of the coronary ostia.

L. N. K.

Kalter, S.: The Glycocoll Metabolism in Degenerative Dystrophic Heart Disease. *Deutsche Med. Wchnschr.* 62: 1371, 1936.

In a series of cases of myodegeneratio cordis, 5 grams of glycocoll was given 3 times daily. This caused improvement of the heart function in most cases.

L. N. K.

d. Gara, P.: Clinical Observations in the Treatment of Heart Disease With Gratusbaina and With Gratusbainose. *Med. Welt.* 10: 1296, 1936.

They have a diuretic action. It is claimed that they make the pulse regular, raise low blood pressure, and lower high blood pressure (?).

L. N. K.

Beer, A. G.: Indication and Action of Scillagluco-side. *München. med. Wchnschr.* 83: 929, 1936.

This presentation is based on a study of 123 cardiac patients. The cardiac action of this glucoside is less than that of strophanthin but its action in sup-



pressing the ectopic pacemakers is greater. It is quickly absorbed and quickly destroyed on oral or rectal administration as compared with other digitalis preparations.

L. N. K.

Donath, F.: Therapy of Acute Coronary Closure. *Wien. klin. Wchnschr.* 49: 692, 1936.

The author uses morphine together with caffeine and atropine as soon as the diagnosis is made. Morphine is repeated if necessary, and other narcotics such as pernocton are used. The author treats the stage with a drop in blood pressure with camphor, caffeine, strychnine, cardiazol, or coramin. During the healing stage, the patient requires six weeks' bed rest. No medication is necessary but euphylline may be used. Luminal to ensure sleep should be employed if necessary.

L. N. K.

## PROCEEDINGS OF THE GERMAN SOCIETY FOR THE STUDY OF CIRCULATION

TENTH SESSION, BAD NAUHEIM, MARCH 13 AND 14, 1937\*

### 1. Vasodepressor Substances. H. Dale (London).

While a number of vasodilator substances derived from tissue extracts are known, there is no direct evidence of their playing any rôle in physiological regulation of vessel tone. Histamine is the first substance isolated and has recently been shown to act by stimulating the sensory nerve endings. Acetylcholine works directly on the cholinergic efferent nerve endings. Since histamine is so powerful, it must exist in the body in a bound form. The histamine in plasma comes from the body cells. The acetylcholine found in the blood plays little or no rôle normally. The increase in flow of blood during activity must depend on liberation of vasodilators in the contracting muscle. Knowledge concerning adenylic acid derivatives is still fragmentary and the same is true of other dilators since it is difficult to free them from histamine.

### 2. Adrenalin and Adrenalin-like Substances. H. Bein (Göttingen).

The confusion regarding adrenalin is due to the fact that it has been used too often in pharmacological rather than physiological doses. Adrenalin has a vasoconstrictor action and also increases the blood volume. Its significance is doubted as a normal regulator of the circulation. It is found that painful stimuli do lead to liberation of adrenalin, but whether this is of significance is yet unknown. It is possible that adrenalin in physiological doses acts to redistribute blood in the body. This is true in the case of exercise where the distribution between active and inactive muscle may be aided by adrenalin. Physiological doses of adrenalin cause an emptying of the blood reservoirs. In the heart-lung preparation, no effect could be demonstrated on the metabolism when physiological doses of adrenalin were used. Thus, adrenalin in physiological doses is not a circulatory stimulator but a circulatory regulator to make the distribution of blood more economical. In this, its action summates with nerve stimulation and with that of local metabolic products.

*Fleisch* (Lausanne) in commenting on these reports, pointed out that acetylcholine in the blood comes from active muscles. It appears whenever the blood pressure drops and at the death of the animal. It is thus a pathological sign.

\*Abstracted from report by H. Bruner in *Ztschr. f. Kreislaufforsch.* 29: 329, 1937.

3. Cystamin, a New Histamine-Like Blood Pressure Depressor Substance. H. Robbers (Mannheim).

This is decarboxylated cystin. It causes a drop in blood pressure and acts on peripheral vessels. Subcutaneously, it causes a long lasting effect.

4. Coronary Insufficiency Following Histamine Collapse and Orthostatic Collapse. H. Meessen (Freiburg i. Br.).

Intravenous injections of histamine in large doses caused electrocardiographic changes in the rabbit such as are seen in coronary insufficiency. This is true also in orthostatic collapse. At necropsy, in the latter condition, disseminated myocardial necrosis appears twenty hours later. The redistribution of blood occurring in these two conditions leads to anoxia of the heart.

5. Adrenals and Angina Pectoris. W. Raab (Vienna).

It was found that anginal attacks can be precipitated in young healthy individuals by injections of adrenalin.

6. Circulatory Disturbances and the Function of the Adrenal Cortex. S. Thaddea (Berlin).

In cats the removal of the adrenals leads to bradycardia and a blood pressure drop which is relieved by adrenal cortex. In the heart-lung preparation of the dog, the cortical hormone decreases coronary flow. Electrocardiographic changes following extirpation of the adrenals; viz., S-T depression and T-wave inversion, tend to disappear after cortical hormone administration. Similar results are obtained in Addison's disease.

7. Paraganglia in the Sympathetic System and in Cranial Nerves. M. Watzka (Prague).

Three groups of paraganglia are found: chromaffine, nonchromaffine, and mixed. The chromaffine ganglia are sympathetic in origin. The others are of mixed nerve origin. All are rich in nerve fibers.

8. Action of Strophanthin on the Circulation of Normal Persons. K. Gotsch (Prague).

It is found that stroke and minute volume of the heart decreases when this drug is used on normal persons. By direct intraarterial injection and comparison with the control limb, it could be demonstrated that strophanthin increases  $O_2$  consumption in the periphery.

P. Martini (Bonn) found an increase in stroke and minute volume flow with this drug.

9. Pharmacology of Coronary Insufficiency. C. Kroetz (Altona).

He believes that a combination of drugs is indicated for daily use; viz., quinine, luminal, and nitrite by injection. This combination is especially valuable in severe status angiosus and in cardiac asthma. He advocates vitamin  $B_1$  in myocardial infarcts and also points out the value of a pure preparation of glutathione which acts as a cardiac stimulant and coronary dilator.

A. Weber (Bad Nauheim) noted the fact that coronary insufficiency sometimes is clinically and electrocardiographically silent.

Heubner (Berlin) was opposed to the use of combinations of drugs.

10. Heart and Circulation in Emphysema and Bronchial Asthma. A. J. Anthony (Grissen).

No evidence of heart damage was noted clinically or in the electrocardiogram. At autopsy the heart showed disseminated degenerative changes which extended to the endocardium and caused mural thrombi. The histological changes resemble those seen in rabbits following caffeine and adrenalin. Suspicion is aroused that in man the common use of the drugs is the cause of these changes.

*E. Kirch* (Erlangen) pointed out that hypertrophy of the right heart can be demonstrated postmortem in emphysema.

11. The State of Circulation and Breathing of Man at Low Pressures. K. Matthes (Leipzig).

An increase was noted in minute volume flow in the decompression chamber when the atmospheric pressure was lowered. No change occurred in circulation time from the lung to the extremities, hence the increased blood flow must be confined to the visceral organs.

12. Effect of Anoxemia on the Venous Pressure of Healthy Individuals. G. Budelmann, A. J. Anthony, and W. Schwarz (Hamburg).

Arterial anoxemia in reclining persons whether produced in decompression chamber or by breathing air with reduced  $O_2$  content, causes a rise of venous pressure up to 5 cm.  $H_2O$ . The authors do not attribute this to heart failure but to a reflex action on the peripheral circulation. When collapse occurs and arterial pressure falls, venous pressure rises further.

13. The Blood Flow in the Veins Near the Heart. E. Holzlöhner (Kiel).

A new electrical tachograph was used for blood flow recording and a tachyogram of venous flow was obtained. A systolic acceleration in flow toward the heart was noted.

*W. Böhme* (Rostock) reported a confirmation of Holzlöhner's observations on venous flow in man based on his roentgenokymographic studies of movement of the heart base when the mitral valve was calcified. In animals he obtained similar data by injecting x-ray opaque materials in the circulation and making roentgenokymographs. He noted the marked movement of the A-V floor. In man iodol drops were injected into the veins and a systolic acceleration in their movement was noted.

14. Effect of the Carotid Sinus Reflex on Circulation, Respiration, and Metabolism. E. Koch, and H. Bräuer (Bad Nauheim).

Long continued stimulation of pressor receptors of the carotid sinus causes alteration of breathing and decreases the metabolism of animals.

15. Hypophysis and Circulation. F. Schellong (Heidelberg).

This is an interesting theoretical discourse. The posterior lobe of the pituitary liberates vasopressin and causes a "pale" hypertension, but the part played in this by central reflex action and kidney damage is not clear. A decrease in vasopressin causes a loss of capillary tone and a drop in diastolic pressure. Functional disorders of the basophilic cells of the pituitary can cause a drop in diastolic pressure such as is seen in Basedow's disease. No evidence is present of a regulatory rôle for vasopressin. In pituitary hypotonia, it is the anterior lobe which is affected. He be-

believes that the hypotonia of hypopituitary origin (anterior lobe) acts via the adrenals. In this condition there is found an inability to adjust the blood pressure to stresses such as standing and exertion.

Cushing's syndrome is discussed, and it is suggested that the adenoma may cause an increase in vasopressin, it may act on the hypothalamic centers, or may cause an increase in the corticotropic hormone and this in turn stimulates the adrenal cortex.

The rôle of the pituitary in essential hypertension is discussed, and it is concluded that it is not primarily concerned, although it may play a subsidiary rôle in determining the constitutional disturbances which lead to the condition. The rôle of the basophilic cell hypertrophy in this condition is not settled.

**16. Hormones and Circulation in Gynecology. W. Haupt (Jena).**

Sex hormones play an important rôle in women, viz., in the menstrual cycle and menopause. Hormones are also important during pregnancy. In addition there is a great change in the circulation in pregnancy due to the need of supplying blood to the placenta. In eclampsia an increase can be demonstrated in vasopressor and antidiuretic substances of pituitary origin. They may be responsible for the symptoms, but this has not been established.

**17. Circulation in Disturbances of Blood Sugar Regulation. M. Bürger (Bonn).**

Small doses of hypertonic sugar appear to relieve spastic states perhaps by liberating a vasodepressor substance from the tissues. In tumors of the adrenals, hypertension, hyperglycemia, and glycosuria occur which disappear when the tumor is removed. Hypoglycemia has been reported in Addison's disease. The pancreas produces a sugar regulating hormone, insulin, and extracts from it give substances on the acting circulation, vagotonin and kallikrein. In young diabetics there is a hypotension. Hypertension occurs in elderly diabetics, and many of these are insulin resistant. The author believes that the latter state is due to a slowed circulation. In hypoglycemic shock the blood pressure drop is due to peripheral dilatation (chiefly in the capillaries). It is important to differentiate this state from diabetic coma. In lesser degrees hypoglycemic shock causes tachycardia, palpitation, headache, and irritability.

**18. Circulation in Thyroid Disturbances. G. W. Parade (Breslau).**

The thyroid operates through its regulation of the body metabolism. It acts also over the sympathetic nervous system. In myxedema there is a slowed circulation, a small pulse pressure, a decreased tone of the heart, and a flattening of the P- and T-waves in the electrocardiogram. In hyperthyroidism, the minute volume flow is increased, partly reflexly and partly by the local increase in metabolism. Sinus tachycardia is due to an adjustment of the nervous balance.

**19. Effect of Puberty on the Blood Pressure. P. Schenk (Danzig).**

He points out the hormones play a rôle in this period.

**20. So-called Pigment of the Heart Muscle and Skeletal Muscles and Its Relation to Muscle Function. R. Bohmig (Rostock).**

Microscopic investigation of the distribution and quantity of lipofuscins in human and ox hearts and in their skeletal muscles is reported. In the atrophic muscle a decrease is shown in the quantity of this pigment. In the heart there is more of this pigment beneath the endocardium than beneath the epicardium. This is the reverse of vitamine C distribution.

21. Determination of the Surgical Approach to Peripheral Vascular Disease. H. W. Passler (Heidelberg).

Acetylcholine is used to determine the functional and organic components in peripheral vascular disease, in order to predict the value of sympathectomy in the case.

22. Electrocardiographic and Kymographic Studies on Athletes After Exertion. H. Reindell (Freiburg).

A prolongation of A-V conduction time was found in most athletes. Also, a prolongation of systole was noted. The roentgenkymogram shows characteristic changes. Following exercise systole is shortened.

Frey (Bern) pointed out that sports lead to right ventricular dilatation.

Stachelin (Basel) pointed out that depression of the diaphragm in athletes can alter the electrocardiogram and x-ray film.

23. Calculations on the Basis of the Probability Theory of Parasystole in Auricular Fibrillation. S. Koller (Bad Nauheim).

This presentation is theoretical.

24. A Tension Electrocardiograph for Quantitative Work for the Practitioner. K. Gross (Erlangen).

25. Unipolar Leads of the Electrocardiogram. R. Schwab (Würzburg).

Two points with maximum potential can be found on the chest, but these are not indications of the right and left ventricle respectively. In unipolar leads from the anterior surface of the heart in animals, all initial complexes show a general similarity, and there is no difference between the two ventricles.

E. Koch (Bad Nauheim) suggested the use of the entire body surface as the indifferent electrode.

L. N. K.

# PROCEEDINGS OF THE GERMAN SOCIETY OF INTERNAL MEDICINE FORTY-NINTH SESSION, WIESBADEN

MARCH 15 TO 18, 1927\*

1. Action of Digitalis on the Central Nervous System. Marx (Berlin).

This central action is indicated by (a) the improvement noted clinically when the blood flow is normal, (b) its stimulating (cafein-like action) in shock, (c) the antipyretic action of digitalis; this occurs also in noncardiacs. Injections of small doses of strophanthin into the ventricle of the brain of the dog causes sinus tachycardia, ventricular extrasystoles, ventricular tachycardia and ventricular fibrillation and death. Eripan injections tend to prevent these effects. The action of digitalis injected into the cerebral ventricles is 10 or 100 times more powerful than when used intravenously. Sectioning the vagi does not always abolish this action of digitalis so that the sympathetic nerves as well as the vagi serve as efferent paths.

\*Abstracted from a report by K. Seggel in *Ztschr. f. Kreislaufforsch.* 29: 225, 1927.

2. Experimental Studies of Coronary Dilator Substances. Frey and Hess (Freiburg).

A Rein stromuhr was used to measure flow in the right coronary artery at the same time that arterial blood pressure was determined in dogs anesthetized with morphine and pernocton. Sugar, papavydrin, novophyllin, cardiotrat, and deriphyllin cause an increased coronary flow and a drop in blood pressure, hence their action is dilator. The latter two have the longest action and are useful clinically.

3. Clinical Studies on the Partial-Electrocardiogram in Man. Ernst (Tübingen).

This is a procedure introduced by F. Groedel for obtaining precordial leads. It permits, in the author's opinion, localization of lesions to one or another ventricle. (This is not convincing.) Sometimes it shows electrocardiographic changes when none are present in the limb leads.

4. The Stimulating Substance in Hypertension, Its Properties and Action. Westphal and Sievert (Hannover).

It was found that the ultrafiltrate of the blood of 150 patients with hypertension has a pressor action in cats, rabbits, dogs, and humans. Its action is peripheral; it resembles the pressor substance obtained from the posterior lobe of the pituitary. When 2 c.c. of ultrafiltrate was given daily to rabbits, a protracted hypertension, a hypertrophy of the adrenals, and an increase of its cholesterol content was observed in these animals. The rise in blood pressure in rabbits is 50 mm. Hg in essential hypertension and little in the renal form. The rise in the rabbit is proportional to the pressure level in man. In preparing the ultrafiltrate, one must make the blood acid, pH 4, as it is unstable in alkali. It is also unstable in the presence of ultraviolet light. It is adsorbable on talcum, and a second injection is less effective than the first. It is not adrenalin, and it is not the substance isolated by Bohm. It acts in the decerebrated cat, it decreases flow in the perfused rabbit's ear, and it constricts the rabbit's coronary artery.

In the discussion, Volhard (Frankfort) supported this work, but Marx (Berlin), Jores (Hamburg), and Raab (Vienna) questioned it.

L. N. K.

## Book Reviews

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DISEASES OF THE HEART. By Sir Thomas Lewis. 2nd Edition. 295 pages with 45 illustrations. New York, 1937. The Macmillan Company.

In the preface to the first edition Sir Thomas Lewis wrote: "The impulse to write a book of reference has not stirred me, but I have had the desire to place at the disposal of students and medical practitioners the outline of my clinical teaching on diseases of the heart, as this has developed in my talks to my own hospital students. In beginning that teaching twenty and more years ago, I determined that the basis of what I taught should be that which I myself had seen and proved to be true. A second ideal that I have striven hard to attain is simplicity in teaching." This book is more than an outline; it is a study of diseases of the heart in which essentials are emphasized and nonessentials are carefully omitted. Such a book can be written only by one who is a master, and such a book is far more valuable than many volumes of greater length.

The appearance of the second edition is welcomed, not because there are many changes and additions, but because there are few.

Because of the logical arrangement of material and the simple clarity of style this work should be on the required-reading list for all medical writers.

THE DEVELOPMENT OF CARDIAC ENLARGEMENT IN DISEASE OF THE HEART: A RADIOLOGICAL STUDY. By J. H. Palmer, M.D. Special Report No. 222 issued by the Medical Research Council. London, 1937, His Majesty's Stationary Office. Price 1s. 6d. net.

This monograph of some fifty pages presents the results of a radiological study of the progressive changes in the size of hearts, and of their several chambers, the seat of organic disease, and the correlation of these changes with the clinical aspects of the disease. The object in view has been "to study the dynamic process of enlargement in various diseases rather than the static condition of the heart seen at any one stage."

The work was carried on in the cardiac department of the London Hospital under the direction of Dr. John Parkinson.

While the report does not claim to be comprehensive and complete it seems to enlarge the field of usefulness of radiological study in connection with diseases of the heart and gives interesting facts covering the progressive changes in the heart's size in such conditions as persistently increased heart rate, high blood pressure, congestive failure, and coronary thrombosis.

LES MÉTHODES CHIRURGICALES DU TRAITEMENT DE L'ANGINE DE POITRINE: ÉVOLUTION ET RÉSULTATS. By Marcel Bérard (with a preface by Professor René Leriche) 389 pages, Paris, 1937, Masson & Cie.

Dr. Bérard believes that there is a definite place for surgery in the treatment of angina pectoris and that operation should be considered in any case which is resistant to other forms of therapy, except, of course, when there is evidence of cardiac insufficiency. In this volume he discusses the reasons for and results of the various operations that have been suggested or performed for the relief of angina pectoris. After reviewing the anatomy and physiology of the nerves of the heart

and the nature of the anginal attack, he takes up the different operations, which he lists as those having an anatomical basis (that is, those operations that seek to interrupt the pain pathways) and those with a physiological basis (those which aim to interrupt the reflexes initiating an attack or to establish coronary vasodilatation). Of the various procedures he favors stellectomy as performed by Drs. Leriche and Fontaine. He also discusses the possibility of revascularization, citing Beck's work in Cleveland, and total thyroidectomy. He gives brief case reports of thirty cases of total thyroidectomy from the Peter Bent Brigham Hospital and comes to the very definite conclusion that the results of this form of treatment are unsatisfactory.

Dr. Bérard has provided an interesting summary of what has been done or attempted surgically for the relief of angina pectoris. As a summary the book could be greatly condensed with advantage. While angina pectoris is very common, the surgical treatment is relatively unusual, and in spite of this volume and a long bibliography, the final word on the subject has not been spoken.

LES ENDOCARDITES MALIGNES PROLONGÉES. ETUDE ANATOMO-CLINIQUE ET EXPERIMENTALE. By André X. Jouve. 354 pages with 50 illustrations, Paris, 1936, Masson & Cie, price, 50 fr.

The author provides a detailed bacteriological and anatomical study of bacterial endocarditis, considering the lesions of arteries and of other organs as well as those of the heart. He has succeeded in producing the disease in dogs and believes that the experimental findings add to an understanding of the disease in man. The lesions are illustrated by means of photographs and microphotographs, and there is an extensive bibliography.

L'EMBOLIE PULMONAIRE. RECHERCHES CLINIQUES, ANATOMIQUES, PATHOGÉNIQUES ET THÉRAPEUTIQUES SUR LES EMBOLIES ET LES INFARCTUS DU POU MON. By Pierre Bardin. 192 pages with 11 figures and 2 colored plates. Paris, 1937, Masson & Cie, price, 35 fr.

The thesis of this volume is the importance of nervous reflexes in cases of pulmonary embolism. Dr. Bardin notes that sudden death after pulmonary embolism does not bear a definite relation to the size of the vessel occluded and that thoracic surgeons can tie off a large pulmonary vessel without producing sudden death. He believes that when sudden death occurs it is the result of a reflex arising from the effect of embolic material on the nerve endings of the pulmonary arterioles and that a nervous predisposition, a hypervagotonia, is an important factor in this reflex. He believes that with arterial obstruction anywhere in the body the excitation of nerves in the vessel wall is far more important than obstruction to the flow of blood.

Dr. Bardin reviews the experimental work of others and his own work. In dogs he found it practically impossible to produce sudden death from a large pulmonary embolus and he has studied in detail the effect of various procedures designed to alter the neurovegetative or humoral conditions and so to study the reflexes arising from pulmonary embolism under different experimental conditions.

The author also discusses treatment and gives an extensive bibliography. While interesting from an experimental point of view, the book has many weaknesses on the clinical side.

LA DÉRIVATION AURICULAIRE S5 ET LA TRÉMULATION AURICULAIRE. By B. Pinchenzon. Preface by Professor C. Lian. 80 pages. Paris, 1937, J.-B. Baillière et Fils.

Stimulated by his master, Professor Lian, Pinchenzon has written a short book dealing with two subjects; first, the value of a certain electrocardiographic chest lead (called S5); with one electrode over the manubrium sterni and the other at the



inner end of the fifth right intercostal space, in revealing the electrical activity of the auricles when obscurely shown in the classical leads, and second, the clinical analysis of the intermediate stage of the auricular circus movement between auricular fibrillation and auricular flutter, variously labelled in the past as flutter-fibrillation or impure flutter or coarse fibrillation, but which Pinchenzon and Lian would like to establish as a definite electrocardiographic and clinical entity called "auricular tremulation."

The author appends 20 brief case reports and publishes two records showing "auricular tremulation" and one showing "fibrillo-tremulation."

Doctors Pinchenzon and Lian have done us a service in calling attention again to the value of certain chest leads in studying auricular action when the classical leads fail to define it. The very first human electrocardiogram ever published was from a chest lead in the days before the more convenient limb leads were arbitrarily selected. Then later on Lewis and others reintroduced chest leads for the study of auricular activity, but these did not assume any important place in clinical electrocardiography, largely because of the apparent rarity of their need. In this country, the recent introduction of chest leads in routine electrocardiography for the detection of ventricular myocardial disease has proved so important and valuable that the less important chest lead points, such as Lian and Pinchenzon's Lead S5, for the study of the auricles have been overlooked. It may well be that on certain occasions they should be employed, not only this particular lead labelled S5 but others perhaps at various angles to it; other features of auricular activity not clearly shown by Lead S5 might thereby be revealed.

"Auricular tremulation" as a designation for the stage of the auricular circus movement intermediate between auricular flutter and auricular fibrillation does not seem advisable as yet for routine use until further work and experience have proved its value. It may well turn out to be a more satisfactory term than flutter-fibrillation if it can cover the range of circus movements between flutter and fibrillation, but it seems likely that there are still border lines which would have to be designated "tremulation-flutter" or "tremulation-fibrillation." Rather than to introduce a new term for such, why not use as needed the terms we already have, in gradation as follows: flutter, impure flutter, fibrillation-flutter, flutter-fibrillation, coarse fibrillation, and fibrillation. However, the utility and wisdom of such subdivision are frankly open to question. To the reviewer the term flutter-fibrillation is still adequate to cover the range of auricular arrhythmia between flutter and fibrillation. He and most others have employed the term to signify this intermediate mechanism, labelled in this book auricular tremulation, and not to signify alternate periods of auricular fibrillation and auricular flutter which should be designated by point of time, not as a joint arrhythmia.

Fortunately, clinically it is of little importance apparently to identify this particular phase of auricular arrhythmia—tremulation—by a chest lead, for etiologically, prognostically, and therapeutically it appears to have the same significance as auricular fibrillation and auricular flutter and should so be treated, as it doubtless is being treated most of the world over.

However, the skepticism of the reviewer should not by any means be considered as a bar to the further study of auricular action by chest leads or to the analysis of this auricular mechanism intermediate between flutter and fibrillation which Doctors Lian and Pinchenzon have called tremulation, a good term if further study justifies its adoption. A further point of interest in research would be to see if other chest leads at other angles might not reveal, even better than S5, circus waves that might be traveling in planes that are not well represented by S5.

PHYSIOLOGY AND PATHOLOGY OF THE HEART AND BLOOD-VESSELS. By John Plesch. Oxford University Press, London, Humphrey Milford, 1937. 188 pages, price \$5.25.

The title of this book is somewhat misleading. As indicated in the preface, this work does not pretend to the completeness of a textbook. It is a stimulating general discussion of certain important aspects of the field. It represents an individual viewpoint, based on experimental evidence, on mathematical considerations, on teleological argumentation, and here and there on assumption. It is written by one who has had experience in the field and who must have pondered a great deal on the problems discussed. In general, mechanical factors in the regulation of the circulation are overstressed, often at the expense of established nervous and chemical factors. Several correlations not generally recognized are brought out convincingly.

The first four chapters contain discussion on the mechanical reactions of the blood vessels and on the factors regulating blood volume and blood flow. Chapter V, on the physiological relationship between the arteries and the blood pressure, contains original interpretations. Chapter VI, describing the nature of the regulation of the circulation, is the key which is subsequently applied in the interpretation of some of the problems in pathology, such as circulatory insufficiency, diastolic or volume insufficiency, systolic or force insufficiency, and valvular lesions.

There are several statements which are arbitrary assumption and, on the basis of available evidence, obviously incorrect. The following are examples: "The residual volume of the ventricle is taken as constant" (p. 51). The optimistic statement on arteriosclerosis: "Its progress can be arrested; it can be cured in the early stages and beneficially influenced in more advanced cases" (p. 137). The statement that athletes "show marked calcification of their arteries by the age of 35-40. They are seldom capable of great physical effort in middle life, and many of them die about the age of 50" (p. 143). "Many patients diagnosed on auscultatory evidence as aortic insufficiency, coming to post-mortem from some independent cause before the symptoms of insufficiency develop, show stenosis of the valve without any evidence of insufficiency" (p. 148).

The book is not written for the practicing physician or for the average "specialist." Those who are engaged in the study of the physiology and pathology of cardiovascular problems will find in the book an informative and challenging, though at times one-sided, discussion. It is written from a different angle from any of the recent books on the heart or on the circulation. The author has made an effort "to decide whether a certain formulation in mechanical terms provides a good working hypothesis for the prediction of physiological and pathological events" (p. 83).

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## Books Received

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ALLEGEMEINE ELEKTROKARDIOGRAPHIE. von Prof. Dr. Eberhard Koch. Bad Nauheim. 3., verbesserte Auflage. Mit 39 Abbildungen. Dresden und Leipzig, 1937, Verlag von Theodor Steinkopff.

VERHANDLUNGEN DER DEUTSCHEN GESELLSCHAFT FÜR KREISLAUFFORSCHUNG. X. Tagung zu Bad Nauheim Vom 13—14 März 1937. Herausgegeben von Prof. Dr. Eb. Koch, Bad Nauheim. Mit 140 Abbildungen Im Text. Dresden und Leipzig, 1937, Verlag von Theodor Steinkopff.

ARCHIV FÜR KREISLAUFFORSCHUNG. Beihefte zur "Zeitschrift für Kreislaufforschung." Herausgegeben von Dr. Eb. Koch, Professor für Physiologie, Kerckhoff-Herzforschungs-Institut, Bad Nauheim und Dr. Ed. Stadler, Professor, Leitender Arzt am Stadtkrankenhaus, Plauen i. V. Band I. Heft 1-6. Juli 1937. Dresden und Leipzig, 1937, Verlag von Theodor Steinkopff.

LAS MIOCARDITIS. Por El Doctor Gregorio N. Martínez, Profesor Titular de la Facultad de Medicina de Córdoba; Miembro de las Academias de Medicina de Río Janeiro, Madrid y Rumanía; en colaboración con los Doctores S. Sonzini Astudillo y C. Deza Cenget. El Ateneo Librería Científica y Literaria. Florida 371—Sucursal; Córdoba 2099. Buenos Aires. 1937.

EXPLORACION DEL CORAZON POR VIA ESOFAGICA. Tesis de Doctorado por el Dr. Alberto C. Taquini. "El Ateneo" Librería Científica y Literaria. Florida 371—Sucursal; Córdoba 2099. Buenos Aires. 1936.

LAVORI DEI CONGRESSI DI MEDICINA INTERNA. Quarantaduesimo Congresso Tenuto in Roma. Nell'Ottobre 1936. Pubblicazione Fatta per Mandato del Consiglio Direttivo dal Prof. Giuseppe Sabatini. RELAZIONI Ia.

FISIOPATOLOGIA DELLO SCOMPENSO CRONICO DI CIRCOLO. Cesa-Bianchi D. e Calabresi M. (Milano). Roma Casa Editrice Luigi Pozzi. 1936-XIV.

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### Erratum

In the article, "Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs," by Norman E. Freeman, M.D., and Irvine H. Page, M.D., which appeared on page 405 of the October issue of the Journal, the illustrations for Figs. 4, 5, and 6 were incorrectly placed. Figure 4 should have been Fig. 6; Fig. 5 should have been Fig. 4; and Fig. 6 should have been Fig. 5. The legends are correct as numbered and apply correctly to the rearranged illustrations.

# The American Heart Journal

VOL. 14

DECEMBER, 1937

No. 6

## Announcement

THIS is the last issue of the AMERICAN HEART JOURNAL to appear under the editorship of Dr. Lewis A. Conner. Some months ago he tendered his resignation, which was publicly announced at the annual meeting of the American Heart Association in June, and efforts to induce him to reconsider his decision have been of no avail.

Dr. Conner was the first editor of this JOURNAL; under his leadership it has grown steadily in size, importance, and influence until it stands today as the leading journal in its field—one of which the editor, the publishers, and American medicine may well be proud. Those who have known Dr. Conner, and especially those who have been associated with him in his work, can testify to the enthusiasm and devotion with which he pursued his labors, while the JOURNAL itself bears eloquent testimony to his ability and his high aspirations. Although he frequently consulted the Directors of the American Heart Association for advice and criticism, the actual work was performed almost wholly by him, and he deserves the credit for the development, the splendid growth, and the high ideals of the JOURNAL. To say this is not to disparage the contributions of his associate editors through many years, Dr. Evelyn Holt and Dr. Hugh McCulloch, who have given so freely of their time and thought, nor that of Dr. Irving S. Wright, who for the past two years has edited the papers on vascular disease with great knowledge and enthusiasm. Without the devoted support of these able associates Dr. Conner could never have achieved what he has, but they have been the first to praise his leadership, his ability, his wisdom, and his unselfish willingness to share their labor whenever necessary.

The Board of Directors of the American Heart Association, keenly sensible of Dr. Conner's unselfish devotion and magnificent achievement, wish to take this opportunity publicly to express their grateful and lasting appreciation of his almost unique service. It is their belief, shared by all who know him, that the American Heart Association and the AMERICAN HEART JOURNAL have been peculiarly fortunate in having as the first editor a man so highly endowed with the qualities that

have made him a distinguished leader in American medicine. As he relinquishes the editorship of the JOURNAL which he has served so loyally and unselfishly, the American Heart Association through its Board of Directors expresses to him its deep gratitude, its warm hope for many happy years of profitable activity, and its sense of continuing dependency upon his wise counsel.

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The American Heart Association and The C. V. Mosby Company have the honor of announcing that Dr. Conner's successor as editor-in-chief of the AMERICAN HEART JOURNAL will be Dr. Fred M. Smith, Professor of Medicine in the State University of Iowa. There are probably few men in the field of cardiovascular disease who have as many warm friends in the medical profession, and they will rejoice at this recognition of his ability and influence. His many contributions to our knowledge of heart disease and its treatment are so well known throughout this country and abroad that no word is needed as to his qualifications for this distinguished position. He will have as associate editors Drs. Horace M. Korns of Iowa City, Hugh McCulloch of St. Louis, and Irving S. Wright of New York City.

The publishers of the JOURNAL and the Association of which it is the official organ welcome Dr. Smith to his new post, confident of his ability to continue the splendid work of his predecessor, and bespeak for him and his associates the same fine support and cooperation that were accorded Dr. Conner.

H. M. MARVIN.

## Original Communications

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### A STUDY OF THE RENAL ARTERIES IN RELATION TO AGE AND TO HYPERTENSION\*†

ROBERT H. WILLIAMS, M.D., AND TINSLEY R. HARRISON, M.D.  
NASHVILLE, TENN.

THE concept that the kidney is responsible for most of the clinical instances of hypertension was at one time widely held. With the more general use of the sphygmomanometer and following the development of methods of estimation of renal function, it became clear that, while in patients with glomerular nephritis the increase in blood pressure is clearly secondary to renal diseases, the more common types of hypertension are frequently encountered in persons who display only minimal evidence of functional impairment of the kidneys and exhibit no striking gross anatomical abnormalities of these organs at autopsy. Thus the concept of "essential" (i.e., nonrenal) hypertension gradually developed, and most pathologists as well as the great majority of clinicians have accepted this general idea.

Quite recently interest in this question has been again aroused by the work of Goldblatt and his associates,<sup>1</sup> which has been confirmed by several different investigators,<sup>2-5</sup> and which has shown that experimental interference with the renal blood supply in dogs can cause persistent hypertension without evidence of significant change in renal function. Since these animals present a symptom-complex which resembles that of essential hypertension in man and since patients with the latter condition usually display abnormalities in the renal arteries, it appears that the whole subject of the relationship between elevated blood pressure on the one hand and renal arterial disease on the other hand should be investigated further. The present report represents an attempt to approach this problem from the histological standpoint.

#### SELECTION OF MATERIAL

A group of 10 subjects between the ages of fifty and seventy-five years were studied. This age group was chosen as it was wished to note the effects of long-standing hypertension. To study the changes in cases of more rapidly developing and more severe hypertension, a group of 10 subjects with malignant nephrosclerosis were chosen be-

\*From the Department of Medicine, Vanderbilt University, Nashville, Tenn.

†This study was aided by the Division of Sciences of the Rockefeller Foundation.

TABLE I  
CHANGES IN THE RENAL VESSELS AND IN THE GLOMERULI IN RELATION TO AGE AND TO HYPERTENSION

| group                 | AGE (YR.) |        |      | ARTERIAL BLOOD PRESSURE |         | WEIGHT OF BOTH KIDNEYS (GM.) |        |      | WEIGHT OF HEART* (GM.) |        |      |
|-----------------------|-----------|--------|------|-------------------------|---------|------------------------------|--------|------|------------------------|--------|------|
|                       | HIGHEST   | LOWEST | MEAN | HIGHEST                 | LOWEST  | HIGHEST                      | LOWEST | MEAN | HIGHEST                | LOWEST | MEAN |
| Normal blood pressure | 27        | 20     | 23   | 128/82                  | 80/60   | 111/71                       | 360    | 270  | 310                    | 175    | 251  |
|                       | 40        | 31     | 36   | 150/85                  | 95/65   | 117/75                       | 530    | 255  | 850                    | 200    | 266  |
|                       | 73        | 51     | 64   | 130/80                  | 80/40   | 113/68                       | 400    | 235  | 410                    | 200    | 295  |
| Hypertension          | 32        | 21     | 28   | 210/140                 | 160/100 | 182/119                      | 610    | 90   | 600                    | 295    | 407  |
|                       | 40        | 31     | 38   | 250/170                 | 180/120 | 206/144                      | 830    | 220  | 800                    | 400    | 539  |
|                       | 73        | 52     | 67   | 220/160                 | 160/95  | 175/117                      | 400    | 270  | 930                    | 430    | 644  |

\*The values for the weight of the heart of patients with cardiac valvular disease are not included.

†A value of 100 would indicate that all structures showed the change in question to a marked degree. See text for method of calculation.

‡This refers to the average number of glomeruli in a low power field  $1.2 \times 3.2$  millimeters in diameter.

§When the weights of the kidneys are considered this figure is 21.

TABLE I—Continued  
CHANGES IN THE RENAL VESSELS AND IN THE GLOMERULI IN RELATION TO AGE AND TO HYPERTENSION

| GROUP                       |  | DEGREE OF NARROWING† OF RENAL ARTERIAL TREE |         |        |                |         |        |                                     |         |        |                                 |         |        | NUMBER OF GLOMERULI‡ |         |        | PERCENTAGE OF GLOMERULI SHOWING |         |        |      |         |        |                        |  |  |  |  |  |  |  |  |
|-----------------------------|--|---|---------|--------|----------------|---------|--------|-------------------------------------|---------|--------|---------------------------------|---------|--------|----------------------|---------|--------|---------------------------------|---------|--------|------|---------|--------|------------------------|--|--|--|--|--|--|--|--|
|                             |  | LARGE ARTERIES                              |         |        | SMALL ARTERIES |         |        | AFFERENT GLOMER-<br>ULAR ARTERIOLES |         |        | INTRACAPILLARY<br>HYALINIZATION |         |        |                      |         |        | THICKENING OF<br>CAPSULE        |         |        |      |         |        | CONTRACTION OF<br>TUFT |  |  |  |  |  |  |  |  |
|                             |  |   |         |        |                |         |        |                                     |         |        |                                 |         |        |                      |         |        |                                 |         |        |      |         |        |                        |  |  |  |  |  |  |  |  |
|                             |  |   |         |        |                |         |        |                                     |         |        |                                 |         |        |                      |         |        |                                 |         |        |      |         |        |                        |  |  |  |  |  |  |  |  |
| HIGHEST                     | LOWEST   | MEAN  | HIGHEST | LOWEST | MEAN           | HIGHEST | LOWEST | MEAN                                | HIGHEST | LOWEST | MEAN                            | HIGHEST | LOWEST | MEAN                 | HIGHEST | LOWEST | MEAN                            | HIGHEST | LOWEST | MEAN | HIGHEST | LOWEST | MEAN                   |  |  |  |  |  |  |  |  |
| Normal<br>blood<br>pressure | Young  | 6.7   | 0       | 1.7    | 8.0            | 0       | 1.3    | 0                                   | 0       | 0      | 0                               | 67      | 40     | 47                   | 1.3     | 0      | 0.3                             | 1       | 0      | 0.3  | 0.7     | 0      | 0.1                    |  |  |  |  |  |  |  |  |
|                             | Inter-<br>mediate                                    | 37.3  | 0       | 19.0   | 16.0           | 4.0     | 8.0    | 8.0                                 | 0       | 2.7    | 0                               | 53      | 28     | 43                   | 3.3     | 0      | 1.0                             | 1.3     | 0      | 0.6  | 1.3     | 0      | 0.3                    |  |  |  |  |  |  |  |  |
|                             | Elderly  | 67.0  | 36.7    | 48.3   | 78.7           | 18.7    | 40.0   | 42.7                                | 1.3     | 13.3   | 0                               | 46      | 24     | 35                   | 56.3    | 5.3    | 17.3                            | 23.7    | 2.7    | 8.0  | 25.7    | 0.7    | 8.3                    |  |  |  |  |  |  |  |  |
| Hyper-<br>tension           | Young:<br>glomerular<br>nephritis                    | 36.7  | 0       | 15.0   | 50.3           | 0       | 28.7   | 70.7                                | 9.3     | 42.0   | 0                               | 80      | 25     | 49§                  | 97.0    | 36.0   | 79.3                            | 45.0    | 2.7    | 15.3 | 21.3    | 3.7    | 8.7                    |  |  |  |  |  |  |  |  |
|                             | Interme-<br>diate:<br>malignant<br>hyper-<br>tension | 73.3  | 36.7    | 55.0   | 93.3           | 74.7    | 83.7   | 87.3                                | 38.0    | 65.0   | 0                               | 50      | 14     | 30                   | 87.3    | 46.3   | 59.3                            | 34.7    | 10.3   | 24.3 | 36.7    | 8.3    | 22.3                   |  |  |  |  |  |  |  |  |
|                             | Elderly:<br>benign<br>hyper-<br>tension              | 90.0  | 20.0    | 52.7   | 97.3           | 28.0    | 70.7   | 74.0                                | 29.3    | 57.7   | 0                               | 39      | 19     | 28                   | 97.0    | 20.7   | 45.3                            | 48.0    | 12.7   | 24.3 | 28.0    | 3.0    | 16.3                   |  |  |  |  |  |  |  |  |

\*The values for the weight of the heart of patients with cardiac valvular disease are not included.

†A value of 100 would indicate that all structures showed the change in question to a marked degree. See text for method of calculation.

‡This refers to the average number of glomeruli in a low power field 4.2 x 3.2 millimeters in diameter.

§When the weights of the kidneys are considered this figure is 24.



tween the ages of thirty and forty years. Six patients dying between the ages of twenty-one and thirty-two years with chronic glomerular nephritis were analyzed. (In our limited material we could find only six cases which fulfilled all the requirements.) In choosing the latter group, we believed that (1) the changes associated with essential hypertension could be eliminated, (2) comparisons of the changes in "renal hypertension" could be made with those in "nonrenal hypertension," and (3) involutional changes associated with advancing years would be practically absent.

All hypertensive subjects were chosen with the following requirements:

(1) Systolic blood pressure of 160 mm. or above and a diastolic pressure of 95 mm. or above.

(2) Combined weight of kidneys 220 gm. or more (excluding glomerular nephritic group). (It was believed that the kidneys of essentially normal weight were less likely to show changes due to other causes.)

(3) Weight of heart increased.

Three additional groups of ten subjects with ages corresponding to those above, but showing no evidence of hypertension or renal damage, were chosen to evaluate properly the degree of changes due to the age factor alone.

Patients of the three control groups died of miscellaneous diseases which were infectious in nature in most instances. Uremia was the cause of death in all the patients with glomerular nephritis, with terminal congestive heart failure in four of the six instances. Renal insufficiency was likewise the chief cause of death in eight of the ten patients with malignant nephrosclerosis, congestive heart failure co-existing in five instances. The remaining two patients in this group died of apoplexy. In the older hypertensive subjects renal insufficiency occurred twice but was responsible for death only once, the chief cause of death being congestive heart failure in seven instances, angina pectoris in one, and cerebral hemorrhage in the other.

*Age.*—The ages of the control and hypertensive patients in each of the respective groups corresponded fairly well. There was a slight discrepancy in the young groups.

*Blood Pressure.*—The values of the blood pressures in the control groups and the hypertensive groups were probably lower than would have been encountered while the patients were ambulatory and not in their terminal illness. As would be expected, the highest values were in the malignant group. (The values in Table I for the highest and lowest blood pressures do not represent individual measurements but correspond to the highest and lowest general levels of blood pressure observed in any single patient in the respective groups.)

*Kidney Weights.*—The greatest weights were in the intermediate control group. This was probably due to the fact that the body weight was greatest in this period. It may be noted that the kidney weights of the essential hypertensive groups were approximately normal. Bell<sup>6</sup> has pointed out that in 75 per cent of the patients with essential hypertension the kidneys show no contraction. A significant degree of contraction of the kidneys was found only in the group of glomerular nephritis.

*Heart Weight.*—The heart weight was greatest in cases of benign nephrosclerosis. This was most likely due to the fact that the hypertension in this group had been present over a longer period. That age also played a part is shown by the control group.

#### METHOD OF STUDY AND RESULTS

Routine sections obtained at autopsy and stained with hematoxylin and eosin were studied. In each section were examined ten large arteries (chiefly interlobar), twenty-five small arteries (chiefly arcuate and interlobular), and fifty afferent glomerular arterioles. The amount of thickening of the walls with resulting decrease in size of lumina was classified as normal, slight, moderate, or marked. (Such a method is obviously rough as a quantitative approach, but all the sections were studied by the same observer.) For purposes of comparison the vessels showing slight changes were given the value of  $\frac{1}{3}$ , moderate changes a value of  $\frac{2}{3}$ , and marked changes a value of 1. The numbers were added together for the arteries of a given size in a given section and multiplied by the expression 100/number of arteries counted. Thus, if all the arteries of the group under consideration in a given section showed marked narrowing, the resulting figure would have been 100 and similarly 66.7 and 33.3, if all the vessels had shown moderate or slight narrowing, respectively.

*Large Arteries.*—Although each of the control groups had essentially the same blood pressure, there was a marked increase in sclerosis with advance in years (Table I and Fig. 1). Even though the glomerular group and benign group had the same blood pressure, there was at least three times as much sclerosis in the latter. However, that hypertension also played a rôle in the causation of sclerosis of these arteries was shown by the degree of sclerosis in the malignant group. Considering this and the fact that the glomerular nephritic group showed much more atherosclerosis than its corresponding control group, one would conclude that hypertension was a factor in the production of renal atherosclerosis. Kirkes<sup>7</sup> and later Traube<sup>7</sup> were apparently the first to claim that hypertension produces atherosclerosis. Yet age was the more important factor in causing those atheromatous changes. Since it has been shown that experimental narrowing, by means of the Goldblatt clamp, of

the large renal arteries will produce hypertension in animals, it is reasonable to assume that sclerosis of these vessels in man, if sufficiently advanced, may produce hypertension.

The fact that renal arterial disease may—rarely—be completely absent (Bell and Clawson,<sup>8</sup> Fishberg<sup>9</sup>) in hypertensive patients is not evidence against this view because there is ample evidence that hypertension is not a disease entity but includes a number of different syndromes. The important points are: that renal ischemia can cause hypertension; that renal atherosclerosis is almost universal in subjects of 60 years of age; that it is much more marked in some subjects than in others; and that there is no good evidence against the assumption that it can be responsible for *some* of the cases of hypertension. According to this conception, senile hypertension may in some instances be due not to a disease per se but simply to an exaggeration of a pathological process which occurs in some measure in all subjects with advancing age. The increased degree of arterial disease in the kidneys of hypertensive patients may therefore be explained in two ways: (1) The hypertension increases the strain on the vessels and thereby causes additional disease. (2) The hypertension develops in the first place because the patient has more arteriosclerotic narrowing of the renal vessels than is usual for his age.

According to this point of view, the degree of interference with the renal blood supply must be regarded as of prime importance. Experimentally, one finds that slight constriction of the renal arteries of a dog with a Goldblatt clamp may cause no rise in blood pressure, but, after a certain point is reached, only slight additional constriction is necessary to produce hypertension. That a significant and measurable degree of interference with the renal circulation does exist in certain patients with renal arteriosclerosis is indicated by the work of various authors who have shown by perfusion methods that the resistance in the kidneys is increased in hypertensive subjects and by other investigators who have demonstrated narrowing of the renal vessels by x-ray photographs after injection. (The literature in this regard has been summarized by Fishberg.<sup>9</sup>)

If the opinion advanced above—i.e., that renal atherosclerosis may, when sufficiently marked, be a cause of hypertension—is correct, one would expect that a *vicious cycle* would ensue, the *rise in blood pressure causing more arterial disease, this in turn producing further increase in blood pressure*, etc. Such a conception may possibly account for the progressive nature of glomerular nephritis and of malignant nephrosclerosis once these processes are well established. However, this conception fails to account for the initial rise in blood pressure in young subjects with malignant hypertension and also fails to explain the slowly progressive nature of benign hypertension in the subjects in

whom the initial rise in blood pressure is assumed to be the result of the change in the ageing renal arteries. The slower progression of the disorder in these elderly patients might be accounted for by the assumption that the elderly patient is less sensitive to the same stimulus than the younger subject. An analogy could be drawn here to cardiac

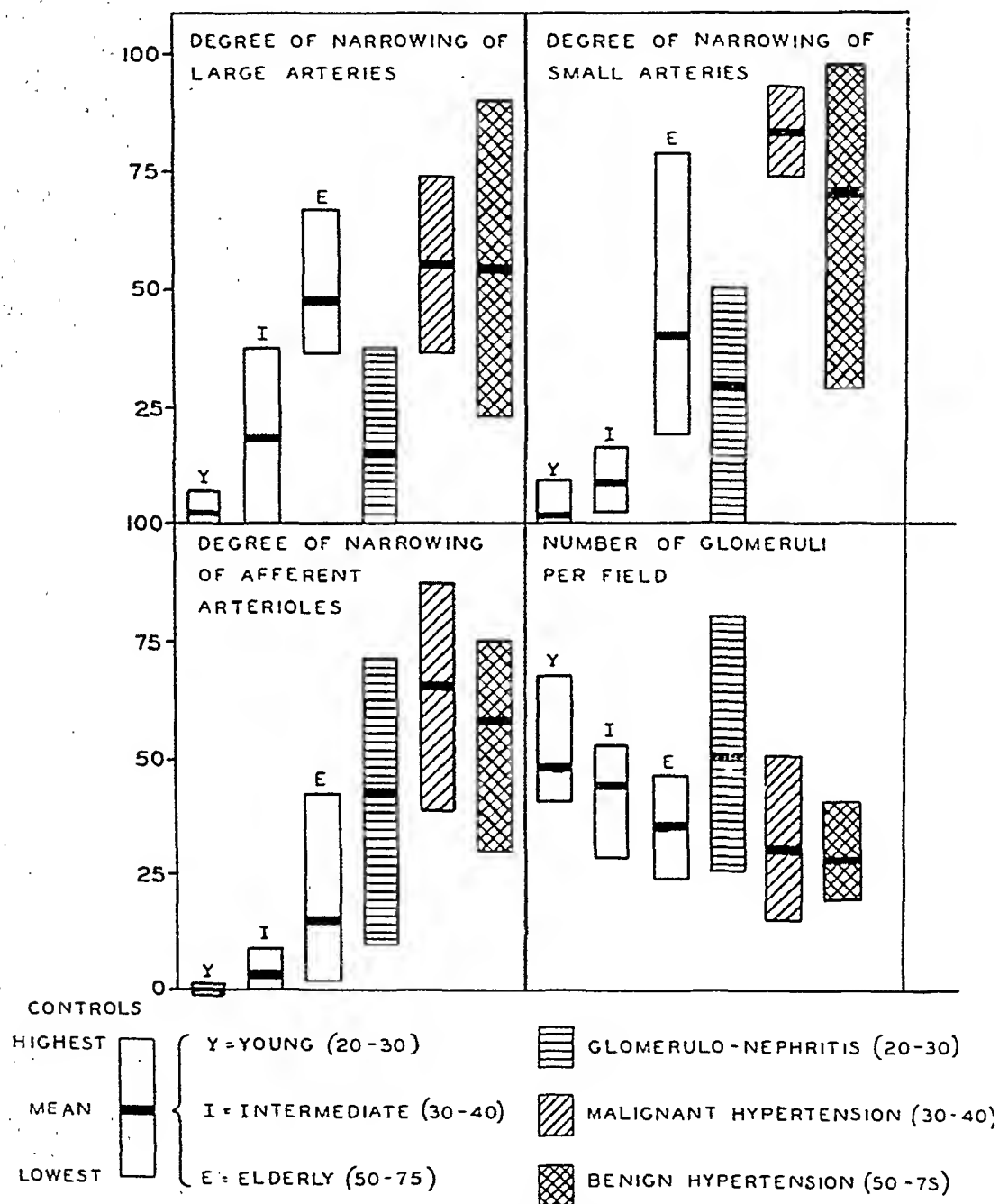


Fig. 1.—The ranges and averages (heavy lines) are shown. The figure shows that narrowing of the large renal arteries is predominantly related to advancing age, while narrowing of the renal arterioles is related chiefly to hypertension. In the case of the small arteries of the kidney both factors are important. There is a progressive decline in the number of glomeruli with advancing years.

dyspnea, for with a given degree of pulmonary congestion, as measured by the vital capacity, a younger person exhibits much greater increase in ventilation and more dyspnea than does an elderly patient. The question whether a given degree of hypertensive stimulus—whatever that

may be—will produce as great a degree of rise in blood pressure in an old subject as in a young one, merits investigation.

*Small Arteries.*—Our results indicate that the changes in the small arteries with advance in age began at a later stage in life, as the intermediate controls showed relatively little sclerosis and the elderly controls showed a relatively large amount. Hypertension seems to have been the more important factor, as the sclerosis was about ten times as great in the malignant group as in the intermediate controls and twice as great as in the elderly controls. The group with malignant hypertension also showed more disease than the group with benign hypertension, even though the subjects of the latter were much older. However, that age was also significant was shown by the fact that the elderly hypertensive group showed more than twice as much sclerosis as the glomerular group, though the blood pressure was the same. In our cases of essential hypertension there was found some sclerosis of the small arteries in every case. Bell and Clawson,<sup>8</sup> studying a large series of hypertensive cases, found that 98 per cent showed some change in these vessels. This change was noted in all but one of our cases of glomerular nephritis, and in this case the hypertension was of much shorter duration than in the other cases. Fishberg<sup>9</sup> noted that it was most likely to be present in long-standing cases.

*Afferent Glomerular Arterioles.*—Although there was a definite increase in sclerosis in this group with increase in age, the latter played a very small rôle as compared with the changes associated with hypertension. There was more than three times as much sclerosis in the glomerular nephritic group as in the elderly controls. The subjects with malignant nephrosclerosis, with the highest blood pressure, showed the most outspoken changes. When allowance was made for the great disparity in the ages, the patients with glomerular nephritis had practically as much narrowing of the arterioles as did the individuals with benign nephrosclerosis, the blood pressure being essentially the same in the two groups. Since in the early stages of hypertension noteworthy changes in the blood vessels may not be found, it is believed that the sclerosis is secondary to the hypertension. This opinion is in accord with those of Fishberg and of Bell and Clawson and is strengthened by the work of Blount,<sup>10</sup> who showed that in amphibian larvae in which vasoconstriction was produced by pituitary transplants increase in the size of the heart preceded hyalinization of the basement membrane of the glomerulus.

However, one cannot attribute all the vascular changes in glomerular nephritis to hypertension because the sclerosis of the glomeruli will cause narrowing of the associated arteriole. The relative rôle of this factor may be determined by comparing the changes in the kidneys with those in other organs.

*Comparison of the Vascular Changes in the Pancreas and Adrenals With Those in the Kidneys.*—As it was desired to compare the vascular changes of the kidneys with those of other very vascular organs, studies were made of the sections of the pancreas and adrenals in five of the previously mentioned elderly subjects and in five of each hypertensive group. Estimations were made of the degree of narrowing of the arterioles in the adrenals and of the small arteries and the arterioles in the pancreas (Table II and Fig. 2).

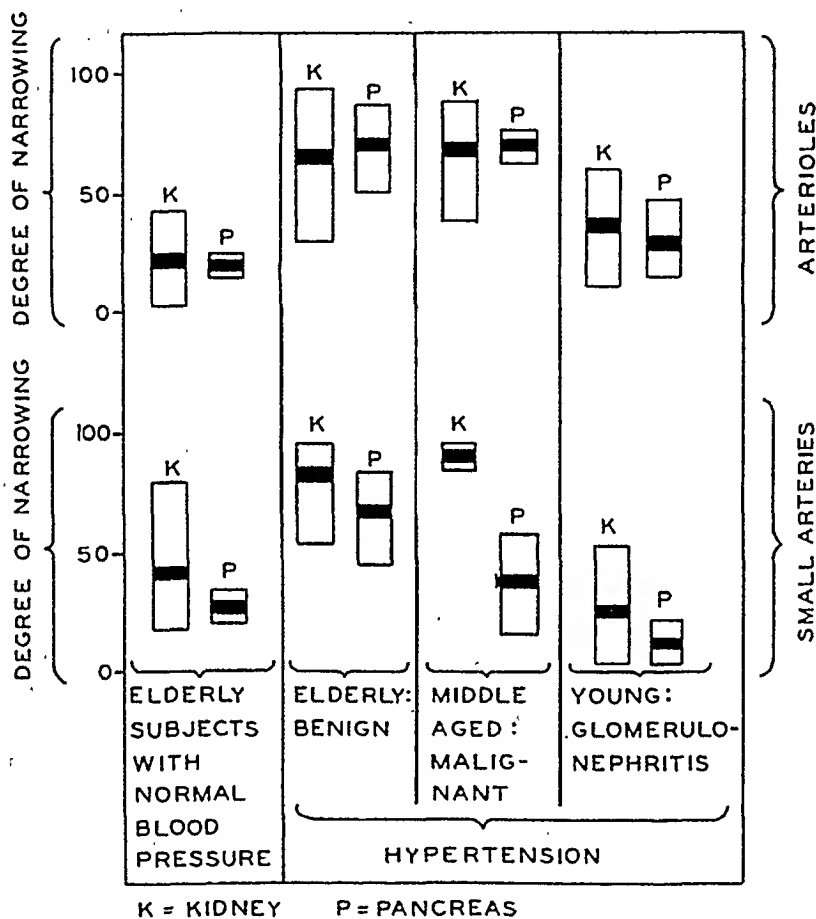


Fig. 2.—In the patients with malignant nephrosclerosis and in those with benign hypertension there appears to be some relationship between arteriolar narrowing and the decrease in the number of glomeruli. No such relationship exists in the elderly control subjects. In none of the groups is there any definite relationship between the degree of narrowing of the large and small arteries and the number of glomeruli.

The changes in the arterioles of the three organs closely paralleled each other.

The small arteries of the pancreas also showed definite narrowing in the elderly controls and in each of the hypertensive groups, but the degree of change was less than that found in the kidneys. Since, on the one hand, there were definite although rather slight changes in the small pancreatic arteries of the young subjects with glomerular nephritis, and since, on the other hand, these vessels also showed definite changes in the elderly control groups, it is evident that in the pancreas

TABLE II

DEGREE\* OF NARROWING OF SMALL VESSELS OF KIDNEY, PANCREAS AND ADRENALS

|  | ARTERIOLES |          |          | SMALL ARTERIES |          |
|--|------------|----------|----------|----------------|----------|
|  | KIDNEY     | PANCREAS | ADRENALS | KIDNEY         | PANCREAS |
| Elderly controls                             | 22         | 20       | 32       | 43             | 27       |
| Elderly subjects: Benign hypertension        | 64         | 70       | 68       | 83             | 67       |
| Middle-aged subjects: Malignant hypertension | 67         | 69       | 72       | 90             | 38       |
| Young subjects: glomerulonephritis           | 36         | 27       | 30       | 25             | 13       |

\*The figures shown represent the average values for five cases. A figure of 100 would indicate that all structures showed marked narrowing.

as in the kidney both age and hypertension may be important factors in the production of degenerative changes in the small arteries.

*Types of Histological Change in the Renal Arterial Tree.*—Thus far we have considered the degree of narrowing, i.e., the quantitative changes in the vessels. Concerning the qualitative changes we have nothing to add to the descriptions already published by Jores,<sup>11</sup> Fahr,<sup>12</sup> Fishberg<sup>9</sup> and Bell and Clawson.<sup>6</sup> As these authors have pointed out, the changes in the large vessels are predominantly atherosclerotic; those in the small arteries consist particularly of hyperplastic elastic intimal thickening (Jores); and the alterations in the arterioles consist in hyalinization, with necrosis in the acute cases of malignant nephrosclerosis. The vascular changes in glomerular nephritis were similar, although less marked, to those in the other two groups of hypertensive patients, except that the change spoken of by Bell and Clawson as regenerative intimal thickening, which they regard as the result of glomerular occlusion and which consists of delicate fibrous tissue rather than coarse lamellae, was relatively more frequent in this group.

*Changes in the Glomeruli.*—A study was made of the qualitative and quantitative changes in the glomeruli associated with advance in age and with the previously mentioned types of hypertension. The sections analyzed were the same as those used for the study of the vascular changes.

Under low power were counted the number of glomeruli in several fields, each  $4.2 \times 3.2$  mm. in area, and the average computed. Allowance was made for the reduction in weight of kidneys in the group of glomerular nephritis. Areas showing marked degrees of scarring were not counted. One hundred consecutive glomeruli were counted under high-power magnification, and the degree of capillary hyalinization, thickening of the capsule, dilatation of the capsule, contraction of the tufts and varying combinations of these were recorded. (A few of these changes are noted in Table I. The values given were obtained by calculations similar to those made in the case of the arteries.)

Varying alteration in the glomeruli was noted. The lakelike dilatation of the afferent arterioles, described by Löhlein<sup>13</sup> as being one of the earliest changes associated with hypertension, was frequently noted. The early changes described by McGregor<sup>14</sup>—hyalinization of the capillary basement membrane of the glomerulus—was also often observed. With progression of the disease there occurred varying degrees of capillary hyalinization, thickening of the capsule, and a gradual contraction of the entire glomerulus. The capillary hyalinization was frequently seen to occur alone. Thickening of the capsule occurred alone but rarely. Dilatation of Bowman's capsule with shrinkage of the glomerular tuft has been an infrequent finding. There were only a few glomeruli that did not show some of these changes. There was much more complete scarring of the glomeruli in the group of glomerular nephritis than in other hypertensive cases. The control group showed these changes to a less degree with advance in age.

Moore<sup>15</sup> found that in both man and rat there was a progressive decrease in the number of glomeruli with advancing years. Although our subjects within a given group displayed wide fluctuations the average figures exhibited this general tendency (Table I and Fig. 1).

As a rule, there were fewer glomeruli per field in the hypertensive subjects than in the control individuals within the same age group. When the weight of the kidneys was taken into account, the glomerular nephritic group showed fewer glomeruli than any. The changes in the control groups were relatively rare.

As shown in Fig. 3, there was no definite relationship of the degree of vascular disease to the number of glomeruli in the case of the large and small arteries, but the hypertensive cases seemed to show a definite decrease in the number of glomeruli with advance of the disease in the arterioles. This decrease may be a result of sclerosis of the vessels with resulting atrophy of the corresponding nephron. On the other hand the sclerosis of the vessels may be secondary to involutionary changes in the glomeruli analogous to those described by Grafflin<sup>16</sup> in the daddy sculpin. He found that glomeruli, while present at birth in these fish, gradually disappeared with advancing age and were practically completely absent in the mature adult forms. Alterations similar to those in the sculpin were occasionally seen in our material. *Post hoc, propter hoc*, it may be conceived that an atrophy of a large number of glomeruli might favor the development of hypertension.

Another change which Grafflin described consisted in a pinching of the neck of the tubule, with blockage and swelling of the glomerular capsule and consequent pressure atrophy of the capillary tuft. This was encountered but rarely in our sections.



## DISCUSSION

The bearing of the findings on the general conception of essential hypertension may now be briefly discussed. The evidence for the existence of essential (i.e., nonrenal) hypertension consists in the occurrence

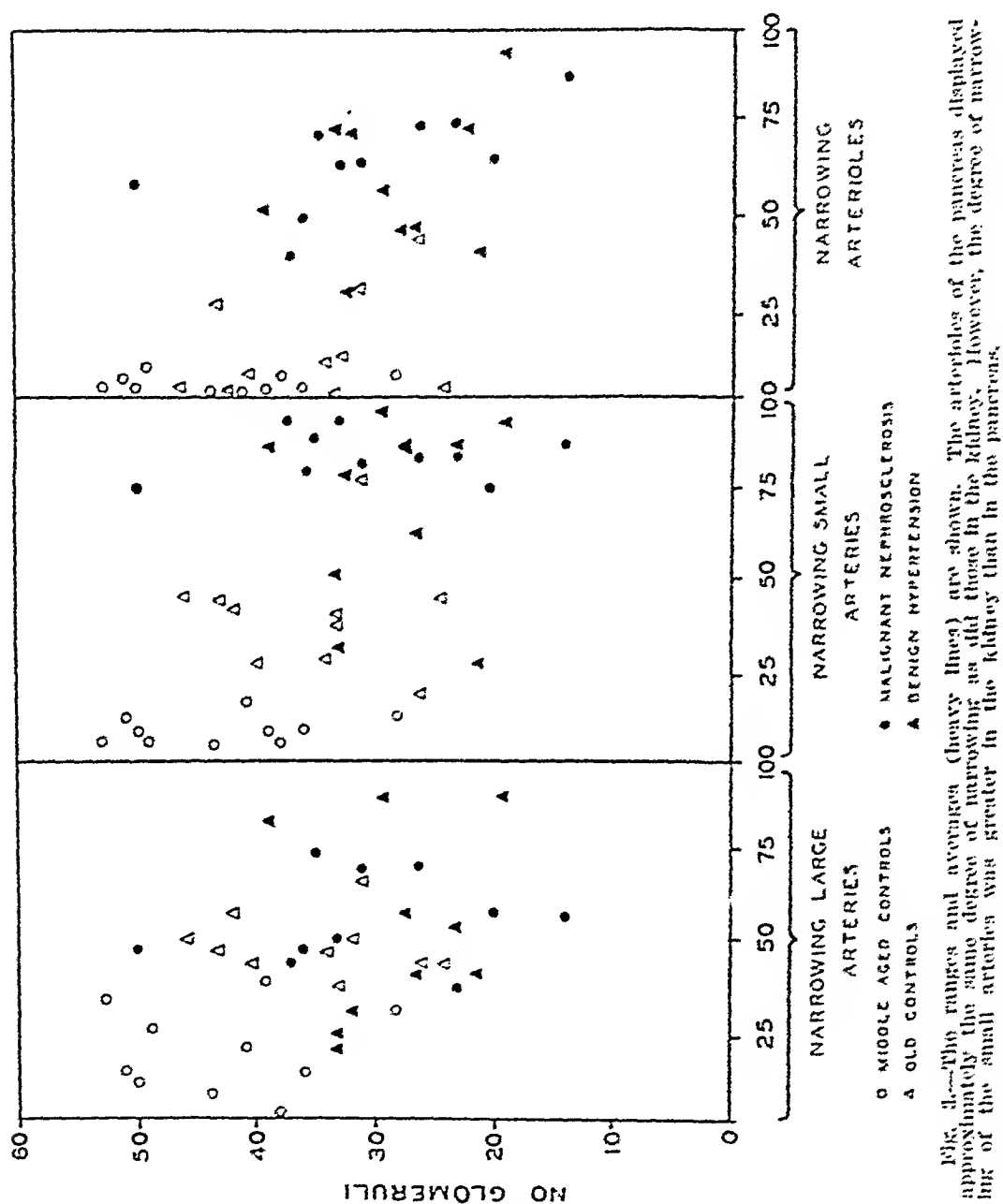


Fig. 3.—The ranges and averages (heavy lines) are shown. The arterioles of the pancreas displayed approximately the same degree of narrowing as did those in the kidney. However, the degree of narrowing of the small arteries was greater in the kidney than in the pancreas.

of a group of patients without a history of antecedent nephritis who present a picture—at least in the early stages of the disease—of elevated blood pressure with no demonstrable impairment of renal function, and who exhibit at necropsy little or no alteration in the gross appearance of the kidney. The clinical evidence is no longer valid, for dogs with experimental renal ischemia and with an increase in blood pressure,

which is obviously of renal origin, may have identical clinical findings. The pathological evidence actually shows that, while in some of the people with essential hypertension changes in the renal vessels may be of such slight degree as to furnish no adequate explanation for the genesis of the increase in blood pressure, in other patients narrowing of the renal vessels similar to but more marked than that which occurs simply with advance in years may be amply sufficient to account for a rise in blood pressure. Such cases are possibly not really essential hypertension at all but belong to the group of renal hypertension, the rise in blood pressure being initially due to a degenerative process in the kidneys rather than to an inflammatory process as in patients with glomerular nephritis.

It is not meant to imply that all essential hypertension is of renal origin. The pathological evidence does not indicate this but only that *some* of such cases *may* be of renal origin. This view is quite different from that advocated by Gull and Sutton,<sup>17</sup> and by numerous later authors, which holds that the increased peripheral resistance of hypertension is dependent on generalized "arteriocalillary fibrosis." It would appear that, when sufficiently advanced, sclerosis of the renal vessels alone can cause hypertension. The rise in blood pressure is clearly not the direct mechanical result of the obliteration of the renal vascular bed, for ligation of the renal arteries does not cause an immediate increase in blood pressure. The mechanism whereby narrowing of the renal vessels produces generalized vasoconstriction remains obscure and requires further investigation.

#### SUMMARY

A quantitative study has been made of the arteries, arterioles and glomeruli, in sections from the kidneys of elderly subjects with benign hypertension, of middle-aged individuals with malignant hypertension and of young persons with hypertension associated with glomerulonephritis. For purposes of comparison sections from the kidneys of nonhypertensive subjects in the same age groups have also been studied. The chief findings and conclusions are as follows:

1. Narrowing of the large renal arteries is predominantly related to advancing age, the degree of change varying markedly in different subjects. Individuals with hypertension exhibit on the average more change in these vessels than do subjects of the same age dying of other diseases.

2. Narrowing of the afferent glomerular arterioles appears to be mainly the result of hypertension, increasing age being a less important factor than in the case of the larger renal arteries.

3. Narrowing of the small renal arteries is related both to hypertension and to increasing age, neither factor being particularly predominant.

4. The small arteries in the pancreas exhibit less marked narrowing than do those of the kidney.

5. The arterioles in the pancreas and those in the adrenals show approximately the same degree of change as do those in the kidneys.

6. With increasing age there is a progressive decrease in the number of glomeruli per microscopic field, the change being more marked in hypertensive than in nonhypertensive subjects. Narrowing of the arterioles and arteries is one factor, but additional factors also seem to play rôles in the diminution in the number of glomeruli. The possibility that involutionary changes, similar to those occurring in certain lower animals, are also concerned is discussed.

#### REFERENCES

1. Goldblatt, H., Lynch, J., Hanzal, R. F. and Summerville, W. W.: Studies on Experimental Hypertension: The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* 59: 347, 1934.
2. Page, I. H.: The Relationship of the Intrinsic Renal Nerves to the Origin of Hypertension, *Am. J. Physiol.* 112: 166, 1935.
3. Collins, D. A.: Hypertension From Constriction of Arteries of Denervated Kidneys, *Am. J. Physiol.* 116: 616, 1936.
4. Elaut, L.: Hypertension arterielle chronique chez le chien par ischemie renale, *Compt. rend. soc. de biol.* 122: 126, 1936.
5. Harrison, T. R., Blalock, A., Mason, M. F. and Williams, J. R., Jr.: The Effects of Extracts of the Kidneys of Normal Dogs and of Dogs With Renal Hypertension on the Blood Pressure of Rats. To be published.
6. Bell, E. T.: The Kidney in Health and Disease, Philadelphia, 1925, p. 292.
7. Kirkes, W. S.: On Apoplexy in Relation to Chronic Renal Disease, *Med. Times and Gazette*, London, N. S. 11: 515, 1855.  
Also: Traube, L.: *Gesammelte Beiträge*, Berlin 3: 164, 1878.
8. Bell, E. T., and Clawson, B. J.: Primary Essential Hypertension: Study of 240 Cases, *Arch. Path.* 5: 939, 1928.
9. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, *Arch. Int. Med.* 35: 650, 1925.
10. Blount, R. B.: Glomerular Basement Membrane of Hypertension in Experimentally Produced Hyperpituitarism, *Anat. Rec.* 65: 1, 1936.
11. Jores, L.: Über die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, *Virchows Arch. f. path. Anat.* 178: 367, 1904.
12. Fahr, Th.: Über Nephrosklerose, *Virchows Arch. f. path. Anat.* 226: 119, 1919.
13. Löhlein, M.: Zur Pathogenese der vasculären Schrumpfare, *Med. Klin.* 12: 741, 1916.  
Idem: Zur vasculären Nierensklerose, *Ibid.*, p. 872.  
Idem: *Ibid.*, p. 1042.
14. McGregor, L.: Histological Changes in Renal Glomerulus in Essential (Primary) Hypertension, *Am. J. Path.* 6: 347, 1930.
15. Moore, R. A.: Total Number of Glomeruli in Normal Human Kidney, *Anat. Rec.* 48: 153, 1931.
16. Grafflin, A. L.: Glomerular Degeneration in the Kidney of the Daddy Sculpin, *Anat. Rec.* 57: 59, 1929.
17. Gull, W. W., and Sutton, H. G.: On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease With Contracted Kidney, *Med. Chir. Trans.* 55: 273, 1872.

## RESULTS FROM TRICHLORETHYLENE INHALATIONS IN THE ANGINAL SYNDROME OF CORONARY SCLEROSIS\*

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IN 1935 Krantz and his coworkers called attention to their experimental work on the pharmacology of trichlorethylene and made the following observations<sup>1-3</sup>: (1) trichlorethylene causes a constriction of the perfused vessels of the frog; (2) it does not affect the consumption of oxygen by rats; (3) it has a variable effect on the coronary blood flow of the dog, at times it increases and at other times it diminishes the blood flow; (4) it decreases the blood pressure and slows the heart rate in dogs; and (5) when applied directly to the sciatic nerve it fails to block the responses of the blood pressure and respiratory system to faradization.

These workers concluded that the drug produces hypalgesia by depressing the basal ganglions and possibly causes a relaxation of the vessels of the splanchnic region while producing peripheral vasoconstriction.

In a recent publication, Love<sup>4</sup> reported his results in the treatment of angina pectoris and coronary thrombosis with trichlorethylene. Twenty-one patients who had the anginal syndrome, including one who had syphilitic aortitis, were treated in this manner. Nine of these patients were said to have had coronary thrombosis at some previous time. Sixteen patients had hypertension. Inhalations were given on the average of three times daily. In eight cases the anginal attacks were completely prevented, in eight other cases the attacks were diminished in severity and frequency, and in one case (syphilitic aortitis) moderate improvement occurred, but antisiphilitic treatment had also been administered. In the four remaining cases no improvement occurred. In three of six cases with coronary thrombosis he claimed to have controlled the pain with inhalations of trichlorethylene at times when administration of opiates had failed to do so.

The interpretation of results in the treatment of the anginal syndrome of coronary sclerosis is extremely difficult and in undertaking to evaluate the merits of any therapeutic program all other modifying procedures must be very carefully considered. Changing the conditions under which the patient lives, such as imposing complete rest in bed or greatly restricting physical activities frequently brings about considerable improvement in the symptoms. Furthermore, individual cases are not strictly comparable owing to the fact that temperament, occupation, habits of life and heredity differ widely in different cases. Likewise, the

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season of the year influences the subjective phenomena of the disease; many patients experience the attacks under less provocation when the weather is extremely cold than they do in the milder seasons of the year.

In undertaking a study of the effect of inhalations of trichlorethylene on the anginal syndrome of coronary sclerosis we were well aware of the difficulties that confronted us in the interpretation of results. We observed forty such patients. The first ones to receive treatment were seen in January, 1936 and the series was concluded in November of the same year, so that sixteen months have elapsed since the beginning and five months since the close of the observation. With only three exceptions, the patients remained ambulatory while under our care. This was done in an attempt to minimize the influence of unusual restrictions, but even so, these patients were away from home and away from their accustomed responsibilities of life and may have been under conditions more conducive to rest and relaxation than would be the case were they treated in their respective communities. They were also perhaps more hopeful as they realized that the form of therapy they were receiving was new in the treatment of an incurable disease.

#### METHOD OF ADMINISTERING TRICHLORETHYLENE

The method of administering trichlorethylene was carried out uniformly in all cases. Glass ampules, each containing 1 c.c. of the drug, were broken in several layers of gauze and the patient, while in the recumbent position, was permitted to inhale the vapor for exactly two minutes. This procedure was carried out morning and evening for the first week. During the second week it was repeated twice daily on alternate days, and from then on, twice daily for two days each week.

This method of administration was arbitrarily chosen, especially with the intent of caution, as we were dealing with a drug regarding which little experience was available as to its more or less prolonged and repeated use. The presumable industrial hazards of trichlorethylene have been reported by Hamilton<sup>5</sup> and by Eichert<sup>6</sup>; untoward reactions appear to follow the use of the unpure preparations of trichlorethylene for commercial purposes.

The immediate subjective effects of the inhalations were variable. Most of the patients experienced transitory light-headedness or giddiness; some became drowsy, and a few lost consciousness briefly before the inhalation was completed. One patient experienced transient visual hallucinations, and saw what appeared to him as myriads of small brightly colored balloons. In only one case did evidence of intolerance to the drug become evident; the patient, who was a man, had a small macular eruption which was distributed diffusely over the body. This appeared on the third day and disappeared when the inhalations were discontinued. Renewed administration of trichlorethylene was well tolerated.

Our observations were limited entirely to patients who had the anginal syndrome of coronary sclerosis (forty cases). The study did not include cases of acute coronary thrombosis although four patients previously had had this condition.

#### RESULTS OF TREATMENT

*Cases in which varying degrees of improvement occurred (eighteen cases, 45 per cent).*—CASE 1. A Jew, aged fifty-seven years, who ran a boarding house, had suffered from anginal attacks for three years. The attacks had recurred three to four times daily after walking only three or four blocks. A roentgenogram showed calcification of the arch of the aorta; an electrocardiogram revealed diphasic T-waves in Lead II, negative T-waves in Lead III and lengthened Q-waves in Lead III. There was no history of previous coronary thrombosis. The value for the systolic blood pressure was 108 mm. of mercury and that for the diastolic pressure was 76 mm. After nine days of treatment, the frequency of the attacks decreased. After the lapse of one year there has been a diminution of both the frequency and the severity of his effort pain, and he is able to walk six to seven blocks without discomfort. Improvement was only moderate.

CASE 2. A Jewish fish merchant, aged forty-eight years, had had anginal seizures for three years. Attacks occurred three or four times daily and he could walk only two blocks without stopping. Roentgenological examination did not disclose any abnormalities; an electrocardiogram showed sinus rhythm and lengthened Q-waves in Lead III. The value for the systolic blood pressure was 134 mm. of mercury and that for the diastolic pressure was 94 mm. The patient has continued with the treatment for nine months. The frequency of the attacks has decreased and he can walk farther than he could before. There was no history of previous coronary thrombosis. Improvement was only moderate.

CASE 3. A physician, aged fifty-eight years, who was a stolid type of individual, had suffered from anginal attacks for one year. The attacks had occurred two to four times daily and he had not been able to walk more than two blocks without stopping. A roentgenogram revealed that the heart was slightly enlarged. An electrocardiogram revealed diphasic T-waves in Lead II, negative T-waves in Lead III, and lengthened Q-waves in Lead III. The value for the systolic blood pressure was 130 mm. of mercury and that for the diastolic pressure was 96 mm. He noted marked improvement after treatment had been given for seventeen days, and fifteen months after treatment was started he was able to resume general practice and at the present time he has only mild attacks after unusual effort. There was no history of previous coronary thrombosis. Improvement was marked.

CASE 4. A farmer, aged sixty-six years, had had anginal attacks for seven years. During the last few months before he came to the clinic the attacks had increased in frequency and severity and the patient was admitted to the hospital in status anginosus. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed diphasic T-waves in Lead I, isoelectric T-waves in Lead II, lengthened Q-waves in Lead III and a delayed P-R interval of twenty-four hundredths of a second. Frequent tracings were not altered. The value for the systolic blood pressure was 120 mm. of mercury and that for the diastolic pressure was 80 mm. The patient gradually improved and eleven months after treatment was started he was doing light farm work in spite of admonitions to the contrary. At present, he experiences attacks which are milder and less frequent than they had been. There was no positive evidence of coronary thrombosis although this condition was suspected at first. Improvement occurred in this case.

CASE 5. A Jewish merchant, aged fifty-one years, had suffered from anginal attacks for one year. The attacks had been irregular in occurrence but usually had appeared several times daily, after moderate activity. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 132 mm. of mercury and that for the diastolic pressure was 88 mm. There was no history of coronary thrombosis. The patient obtained complete relief from the attacks and he can now walk a mile. Treatment was continued after sixteen months.

CASE 6. A man, aged sixty-five years, who was an educator and of an intensive type, had experienced anginal attacks for six years. The attacks had occurred daily after moderate effort. Roentgenological examination disclosed no abnormality. An electrocardiogram showed negative T-waves in Lead I. The value for the systolic pressure was 172 mm. of mercury and that for the diastolic pressure was 118 mm. Treatment has been continued for thirteen months and the patient says he has derived remarkable improvement from it. He now experiences only occasional mild discomfort. There was no history of coronary thrombosis.

CASE 7. A janitor, aged sixty-five years, had had anginal attacks for eight months. During the last two months before he came to the clinic the attacks had become more frequent and more severe than they had been and he was admitted to the hospital in status anginosus. Roentgenological examination disclosed no abnormality. The electrocardiogram showed diphasic T-waves in Leads I and II and negative T-waves in Lead III. There was no alteration on subsequent occasions. The value for the systolic blood pressure was 148 mm. of mercury and that for the diastolic pressure was 96 mm. The patient showed gradual improvement and now, after fifteen months, has only occasional mild attacks. There was no positive evidence of previous coronary thrombosis although this condition was suspected at first. Definite improvement occurred in this case.

CASE 8. A physician, aged sixty years, had experienced an anginal syndrome for ten years. The attacks had occurred once or more daily if he had hurried. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 120 mm. of mercury and that for the diastolic pressure was 80 mm. Treatment has been continued, and after a year the attacks are less frequent and are less severe than they had been. There was no history of coronary thrombosis. Moderate improvement occurred in this case.

CASE 9. A farmer, aged fifty-five years, had had anginal attacks for nine months. He had had daily attacks and had been able to walk only three blocks without pain. Roentgenological examination showed that the heart was slightly enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 164 mm. of mercury and that for the diastolic pressure was 88 mm. He has continued treatment for eight months, and recently reported that his condition was improved. He now can walk half a mile without provoking an attack. There was no history of coronary thrombosis.

CASE 10. A Jewish peddler, aged fifty-six years, had had anginal seizures for two years. He had been able to walk only one block without pain and the attacks had occurred daily. A roentgenogram showed slight calcification of the aorta. An electrocardiogram was normal. The value for the systolic blood pressure was 114 mm. of mercury and that for the diastolic pressure was 78 mm. Seven months after treatment was started the patient reported that his condition was improved, but that he still experienced painful attacks as a result of effort. He now can walk further than he could. There was no history of coronary thrombosis. Slight improvement occurred in this case.

CASE 11. A man, aged forty-nine years, who was an insurance agent, and of a very apprehensive type, had had anginal attacks for four years. He had experienced at least three attacks daily and they had occurred especially after moderate effort and after meals. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 138 mm. of mercury and that for the diastolic pressure was 84 mm. He has continued the treatment for nine months and reports that he is more active than he had been and that the frequency of the attacks has decreased. There was no history of coronary thrombosis. Moderate improvement occurred in this case.

CASE 12. A merchant, aged fifty-seven years, had had anginal attacks for one year. The attacks had occurred daily and had been brought on by walking two blocks. A roentgenogram showed calcification of the arch of the aorta. An electrocardiogram revealed low voltage T-waves in Lead III. The value for the systolic blood pressure was 122 mm. of mercury and that for the diastolic pressure was 74 mm. He has continued treatment for five months and reports that his activities have been definitely increased when he is not under the stress of his business. There was no history of coronary thrombosis. The improvement in this case was questionable.

CASE 13. A physician, aged fifty years, had had an attack of coronary thrombosis three years before he came to the clinic and had had severe recurrent anginal seizures since. He had been completely incapacitated. He had been unable to walk a block and a half without pain. A muscle flap operation had been performed but painful seizures had continued to recur. Roentgenological examination did not disclose any abnormality. An electrocardiogram revealed diphasic T-waves in Lead III and lengthened Q-waves in Lead III. The value for the systolic blood pressure was 116 mm. of mercury and that for the diastolic pressure was 84 mm. While the patient has continued to have attacks, they are less frequent and severe than they had been and the nocturnal attacks have ceased. He can now walk four blocks. Treatment has been continued ten months. It is difficult to evaluate the results in this case, owing to the presence of a healed infarction and because an operation which was intended to increase the vascularity of the heart had been performed. Slight improvement occurred.

CASE 14. A physician, aged forty-seven years, had had anginal attacks for thirteen months. Coronary thrombosis had occurred eleven months before he came to the clinic. The anginal attacks had occurred three to four times daily after very slight exertion. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed T-wave negativity in Lead I. The value for the systolic blood pressure was 148 mm. of mercury and that for the diastolic pressure was 108 mm. After the treatment had been employed for six months the patient continued to have attacks of pain but believed that he could walk farther than he could before the treatment was started. At times he can walk as far as a mile and a half. Slight improvement occurred in this case.

CASE 15. A housewife, aged sixty-three years, had had anginal attacks for nine years. She had been unable to walk more than a block at a time without producing pain. A roentgenogram showed the heart was slightly enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 160 mm. of mercury and that for the diastolic pressure was 80 mm. She reported that her condition was improved after treatment had been continued for six months. She still has attacks but they occur less frequently than they did formerly and are less severe. There was no history of coronary thrombosis. Slight improvement occurred in this case.

CASE 16. An unemployed man, aged sixty-six years, had had anginal attacks for a year and a half. Daily pain had been brought on by walking less than two



blocks. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 158 mm. of mercury and that for the diastolic pressure was 78 mm. He has been taking treatment for seven months and recently reported that his condition was slightly improved. The attacks occur less frequently than they did and he now can walk four blocks. Slight improvement occurred in this case.

CASE 17. A man, aged fifty-eight years, who was an executive, had had anginal attacks for a year and a half. He had had attacks daily, and walking three or four blocks had induced the attacks. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 168 mm. of mercury and that for the diastolic pressure was 94 mm. The patient has retired from business and is leading a life of leisure; five months after the treatment was started he reported that his condition was considerably improved. The fact that the patient completely altered his mode of living makes the evaluation of treatment in this case very unsafe. There was no history of coronary thrombosis. Improvement apparently occurred in this case.

CASE 18.—A man, aged forty-six years, who was a druggist, had had anginal attacks for seven years. The attacks had occurred several times daily as a result of very slight exertion or excitement. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 166 mm. of mercury and that for the diastolic pressure was 108 mm. The patient still has occasional attacks but is considerably improved; he has continued treatment for thirteen months. There was no history of coronary thrombosis.

*Cases in which moderate improvement occurred early in the course of treatment but was followed by an aggravation of symptoms while the patients still were undergoing treatment (five cases, 12.5 per cent).—*CASE 19. A Jewish merchant, aged sixty years, had had anginal attacks for fourteen years. During the last few months before he came to the clinic his symptoms had increased in severity and he had not been able to climb a flight of stairs or to walk a block without pain. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed diphasic T-waves in Lead I. The value for the systolic blood pressure was 130 mm. of mercury and that for the diastolic pressure was 80 mm. For three months after the institution of treatment the patient felt greatly improved and was able to walk six to eight blocks without pain. However, following an acute infection of the upper part of the respiratory tract the symptoms have returned in spite of the treatment. There was no history of coronary thrombosis.

CASE 20. A druggist, aged fifty-two years, had had anginal attacks for three and a half years. He had been able to walk only one block without pain. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 186 mm. of mercury and that for the diastolic pressure was 110 mm. For a month the attacks decreased in frequency and severity but with the onset of cold weather the attacks were as severe as they had been. The patient went south and noted improvement again. There was no history of coronary thrombosis.

CASE 21. A housewife, aged fifty-five years, had suffered from anginal attacks for two and a half years. She had had from eight to ten attacks daily after very moderate activity. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram revealed diphasic T-waves in all leads. The value for the systolic blood pressure was 218 mm. of mercury and that for the diastolic pressure was 134 mm. For the first five months after treatment was instituted the patient obtained marked relief, and the frequency of the attacks was decreased

even when activity was increased. However, during the last three months before this paper was written the severity and frequency of the attacks have increased in spite of treatment and decreased activity. There was no history of coronary thrombosis.

CASE 22. A housewife, aged fifty-three years, had had anginal attacks for five years. Two or three attacks had occurred daily, after slight effort. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 132 mm. of mercury and that for the diastolic pressure was 80 mm. The patient felt greatly improved during the first five months of treatment, but since an acute infection of the upper part of the respiratory tract occurred in the winter, she has noted no further relief from treatment, and the attacks are as severe and frequent as they had been before treatment was instituted. There was no history of coronary thrombosis.

CASE 23. A retired Jewish merchant, aged fifty-nine years, had suffered from anginal attacks for twelve years. He had had from five to eight attacks daily; the attacks had occurred when he had walked less than one block. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed diphasic T-waves in Leads I and II. The value for the systolic blood pressure was 126 mm. of mercury and that for the diastolic pressure was 82 mm. The frequency and severity of the attacks were decreased after the first ten days of treatment, but since then it has been necessary to administer from three to ten tablets of glyceryl trinitrate daily. There was no history of coronary thrombosis.

*Cases in which the treatment did not produce any improvement (thirteen cases, 32.5 per cent).—*CASE 24. A banker, aged sixty-eight years, had had anginal attacks for three years. At the time of his visit to the clinic, he was experiencing one to two attacks daily; the attacks occurred after slight effort, particularly after the evening meal. A roentgenogram showed that the heart was slightly enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 180 mm. of mercury and that for the diastolic pressure was 110 mm. There was no improvement whatsoever after treatment had been continued for five months. There was no history of coronary thrombosis.

CASE 25. A merchant, aged fifty-seven years, had had anginal attacks for ten months. He was having two to three anginal attacks daily, after slight effort. Roentgenological examination did not disclose any abnormality. An electrocardiogram showed negative T-waves in Leads I and II and lengthened Q-waves in Lead I. The value for the systolic blood pressure was 106 mm. of mercury and that for the diastolic pressure was 80 mm. He continued the treatment for seven months, but there was no improvement in his condition. There was no history of coronary thrombosis.

CASE 26. A retired mail carrier, aged sixty-one years, had had dyspnea after effort, for one year, and anginal attacks for one week. He had had one or two painful seizures daily, after slight effort. A roentgenogram showed that the heart was slightly enlarged. An electrocardiogram was normal. The value for the systolic blood pressure was 140 mm. of mercury and that for the diastolic pressure was 100 mm. Continued treatment for three months did not produce any improvement. There was no history of coronary thrombosis.

CASE 27. A W.P.A. worker, aged fifty-six years, had had anginal attacks for five weeks. He had had several attacks daily after slight effort. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram revealed T-wave negativity in Lead I and a left ventricular preponderance. The value for the systolic blood pressure was 166 mm. of mercury and that for the diastolic pressure

was 100 mm. Continued treatment for four and a half months did not produce any improvement. There was no history of coronary thrombosis.

CASE 28. A Jewish painter, aged sixty-three years, had had anginal attacks for fifteen months. Walking slowly for only two blocks had precipitated the painful seizures. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram revealed a lengthened Q-wave in Lead I and a left ventricular preponderance. The value for the systolic blood pressure was 154 mm. of mercury and that for the diastolic pressure was 100 mm. He continued treatment two and a half months, without improvement. There was no history of coronary thrombosis.

CASE 29. A Jewish tailor, aged forty-eight years, had had anginal attacks for nine months. The attacks had occurred daily and had been induced by walking only one block. Roentgenological examination disclosed no abnormality. An electrocardiogram showed low voltage T-waves in Leads I and II and iso-electric T-waves in Lead III. The value for the systolic blood pressure was 120 mm. of mercury and that for the diastolic pressure was 80 mm. The patient did not obtain any relief from treatment. There was no history of coronary thrombosis.

CASE 30. A man, aged fifty-six years, who was a clerk, first had anginal attacks eight years before he came to the clinic. At the time that treatment was undertaken he had daily attacks when he walked three to four blocks. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 120 mm. of mercury and that for the diastolic pressure was 92 mm. No improvement occurred after six months of treatment. There was no history of coronary thrombosis.

CASE 31. A physician, aged forty-nine years, had had anginal attacks for five years. The attacks had occurred daily and frequently had been induced by walking three to four blocks. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 190 mm. of mercury and that for the diastolic pressure was 120 mm. After three months of treatment the patient did not note any improvement in his condition. There was no history of coronary thrombosis.

CASE 32. A housewife, aged sixty years, had had anginal attacks for two years. The attacks had occurred daily, after she had walked only one block. Roentgenological examination disclosed no abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 142 mm. of mercury and that for the diastolic pressure was 82 mm. No improvement was noted after three and a half months of treatment. There was no history of coronary thrombosis.

CASE 33. A clergyman, aged sixty-seven years, had had anginal attacks for twenty-two months. The attacks had occurred daily after he had walked only three or four blocks. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 114 mm. of mercury and that for the diastolic pressure was 86 mm. There was no improvement after one month of treatment. There was no history of coronary thrombosis.

CASE 34. A railway clerk, aged thirty-one years, had had anginal attacks three months. Six weeks before he came to the clinic he was said to have had a coronary thrombosis and had continued to have daily attacks of pain after he had walked only two or three blocks. An electrocardiogram was normal, which throws considerable doubt on the diagnosis of coronary thrombosis. Roentgenological examination did not disclose any abnormality. The value for the systolic blood pressure was 160 mm. of mercury and that for the diastolic pressure was 120 mm. The

patient continued treatment two and one-half months but did not obtain any improvement. This patient's attitude was rather skeptical as he was acquainted with the commercial use of the drug.

CASE 35. A farmer, aged fifty-one years, had had anginal attacks for three years. Daily attacks had occurred after he had walked two blocks. Roentgenological examination did not disclose any abnormality. An electrocardiogram was normal. The value for the systolic blood pressure was 150 mm. of mercury and that for the diastolic pressure was 90 mm. There was no improvement after three and one-half months of treatment. There was no history of coronary thrombosis.

CASE 36. A station agent, aged fifty years, had had anginal attacks for eight years. The attacks had occurred frequently and had been induced by walking three blocks. The attacks had started eight years before he came to the clinic, and they had followed coronary thrombosis. Roentgenological examination disclosed no abnormality. An electrocardiogram showed low amplitude QRS complexes in all leads. The value for the systolic blood pressure was 132 to 170 mm. of mercury and that for the diastolic pressure was 90 mm. No improvement was noted after three and a half months of treatment.

*Cases in which death occurred (four cases, 10 per cent).*—CASE 37. A Jewish housewife, aged sixty-three years, had had anginal attacks for fifteen years. The attacks had occurred from two to five times daily after very little exertion. The patient had been forced to live a very restricted life. A roentgenogram showed that the heart was moderately enlarged. An electrocardiogram revealed the presence of complete left bundle-branch block (0.16 second) and diphasic T-waves in Lead I. The patient was definitely improved after four and a half months of treatment, but she died very suddenly at that time at her home. Necropsy was not performed.

CASE 38. A lumber merchant, aged sixty-five years, had had anginal attacks for three years. Daily attacks had occurred after he had walked only two blocks. Roentgenological examination did not disclose any abnormality. An electrocardiogram revealed diphasic T-waves in Lead II and negative T-waves in Lead III. The value for the systolic blood pressure was 120 mm. of mercury and that for the diastolic pressure was 80 mm. The patient continued treatment for nine months without benefit, and then died suddenly at his home. Necropsy was not performed.

CASE 39. A salesman, aged forty-five years, had had anginal attacks for two years. The attacks had occurred daily and after he had walked slowly for a very short distance. Roentgenological examination disclosed no abnormality. An electrocardiogram revealed T-wave negativity in all leads. The value for the systolic blood pressure was 134 mm. of mercury and that for the diastolic pressure was 76 mm. He continued treatment four months, without improvement, and death suddenly occurred at his home. Necropsy was not performed.

CASE 40. A station agent, aged sixty-three years, had had anginal attacks for two years. They had occurred several times daily, after slight exertion. A roentgenogram showed that the heart was slightly enlarged. An electrocardiogram revealed incomplete bundle-branch block, diphasic T-waves in Lead I, and low amplitude complexes in all leads. The value for the systolic blood pressure was 106 mm. of mercury and that for the diastolic pressure was 72 mm. The patient had less pain after one month of treatment but congestive heart failure developed and the patient died in his sleep two and a half months after he started the treatment. Necropsy was not performed.

## SUMMARY

The results of inhalations of trichlorethylene in this series of cases of the anginal syndrome of coronary sclerosis do not permit this method of treatment to be accepted with enthusiasm. In eighteen cases (45 per cent) varying degrees of improvement occurred. However, when these cases are critically analyzed it is found that only one patient obtained complete relief while the others had fewer attacks of less severity.

In five cases (12.5 per cent), temporary improvement was noted but a return of the previous symptoms occurred while the treatment was still in progress. It is possible that these patients became imbued with a new hope in undertaking this treatment and that their primary response was influenced by this attitude. We, however, were very careful not to create any false hopes among the patients treated. They were frankly advised that the procedure was entirely experimental.

In thirteen cases (32.5 per cent) no improvement whatsoever was noted. The patients in these cases received treatment from one to seven months.

Four patients (10 per cent) died during the course of treatment. All deaths occurred suddenly. Two of the patient who died were temporarily improved.

We have already mentioned the difficulties encountered in the evaluation of the results of therapy in the anginal syndrome of coronary sclerosis. This evaluation is based largely on the interpretation of variations in subjective phenomena. We cannot overlook the natural history of the disease or the fact that similar data have been furnished by many individual observers who have used other drugs in the treatment of this disease.

While the results obtained with this method of treatment have been disappointing, it is however a procedure that warrants a trial when the usual therapeutic agents have failed to give relief. In our experience, and according to the method described, the drug is well tolerated and its administration appears to be perfectly safe.

## REFERENCES

1. Krantz, J. C., Jr., Carr, C. J., and Harne, W. G.: Action of Trichlorethylene on Perfused Vessels of the Frog, *Proc. Soc. Exper. Biol. & Med.* 32: 334, 1934.
2. Krantz, J. C., Jr., Carr, C. J., and Musser, Ruth: A Study of the Anesthetic Properties of Trichlorethylene, *J. Am. Pharm. A.* 24: 754, 1935.
3. Krantz, J. C., Jr., Carr, C. J., Musser, Ruth, and Harne, W. G.: A Contribution to the Pharmacology of Trichlorethylene, *J. Pharmacol. & Exper. Therap.* 54: 327, 1935.
4. Love, W. S., Jr.: The Effectiveness of Trichlorethylene in Preventing Attacks of Angina Pectoris, *Ann. Int. Med.* 10: 187, 1937.
5. Hamilton, Alice: *Industrial Toxicology*, New York, 1934, Harper & Brothers, pp. 218-227.
6. Eichert, Herbert: Trichloroethylene Intoxication, *J. A. M. A.* 106: 652, 1936.

## HEMODYNAMIC STUDIES IN EXPERIMENTAL CORONARY OCCLUSION\*

### IV. STELLATE GANGLIONECTOMY EXPERIMENTS

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**B**ASED on certain clinical, anatomical, and experimental considerations recorded in the literature, Cox and Robertson<sup>1</sup> recently reported an experimental study of the effect of stellate ganglionectomy on various hemodynamic functions in dogs. Twenty carefully trained dogs were tested for resting and exercise heart rate, respiratory rate, and blood pressure, and ten of these for cardiac output. All dogs were subjected to ligation of the left anterior descending coronary branch. Prior to coronary ligation, one-half of the dogs were subjected to bilateral stellate ganglionectomy including the removal of several of the upper dorsal ganglia. The surviving dogs were sacrificed several months after the beginning of the experiment, at which time comparisons were made of the size of the infarcts. It was found that occlusion of the left anterior descending coronary branch produced no appreciable differences between the dogs with stellate ganglia intact and those in which they were removed, as regards pulse rate, respiration, or blood pressure. However, the resting cardiac output became persistently elevated in the dogs with intact ganglia, whereas this function was not altered in the ganglionectomized dogs. Death due to ventricular fibrillation immediately after the vascular ligation was less frequent, and the size of the infarcts was generally smaller in the ganglionectomized dogs.

In several recent publications on hemodynamics following acute occlusion of the left anterior descending coronary branch, Gross, Mendlowitz, and Schauer<sup>2-5</sup> have shown that this produces an immediate fall in cardiac output and a delay in cyanide circulation time. Study of control groups in order to determine the effects of anesthesia alone or anesthesia followed by thoracotomy without vascular occlusion, disclosed the fact that the above mentioned hemodynamic changes were greater than could be accounted for by these control procedures, and were consequently due to the vascular occlusion. The pulse rate, venous blood pressure, hemoglobin, erythrocyte count, blood volume, and serum proteins showed no appreciable immediate changes following the vascular occlusion. Experiments on vagosympathectomized dogs indicated

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Aided by grants from the Lucius N. Littauer and Walter W. Naumburg Funds.

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that the immediate fall in cardiac output was cardiogenic and, therefore, was not influenced by the nervous pathways. All the altered functions in these dogs approached or reached normal values by the end of a week after the vascular occlusion. It seemed of interest, therefore, to determine whether stellate ganglionectomy in dogs produces changes in the hemodynamic functions (cardiac output, circulating blood volume, arterial blood pressure, and cyanide circulation time) during the first week following coronary occlusion.

### METHODS

Thirty-six dogs were used for the experiments. In twelve of these the stellate and thoracic (1 to 6) ganglia were removed on both sides in stages (generally within one month). In 24 dogs the ganglia were left intact. These, therefore, served as controls. After recovery from the ganglionectomy, acute occlusion of the left anterior descending coronary branch close to its origin was performed in all dogs by dissection and ligation.

Hemodynamic studies were carried out according to the methods employed by Gross, Mendlowitz, and Schauer.<sup>3</sup> These tests were performed under nembutal anesthesia immediately before ligation of the vessel, one-half hour after ligation, twenty-four hours later and one week later. Ten of the control dogs were from a series previously reported.<sup>3</sup> The remaining control dogs were studied simultaneously with ganglionectomized ones.

One week after the ligation of the left anterior descending coronary branch, the surviving dogs were sacrificed. The left anterior descending branch was probed to ascertain the occlusion, and the size of the infarct was determined by measuring the longitudinal and transverse diameter of the surface of the infarcted area. In order to determine how deep the infarction extended into the myocardium, the coronary vessels were injected under standard conditions with a barium sulfate suspension in gelatine according to the method described by Gross.<sup>6</sup> Roentgenograms were then made of the whole heart and of serial transverse slices 6 mm. thick.<sup>7, 8</sup>

### RESULTS

Of the 12 ganglionectomized dogs, two (16 per cent) died within twenty-four hours after the operation. Six (50 per cent) survived twenty-four hours but died within one week. Four (33 per cent) survived one week and were then sacrificed. The causes of death in the two animals which died within twenty-four hours were heart tamponade due to hemorrhage into the pericardium, and acute cardiac failure, respectively. The causes of death in the remaining animals dying within one week were secondary shock, cardiac failure, and pneumonia. Eliminating from this series those dogs which died from pneumonia or hemorrhage leaves a one-week survival rate of 56 per cent.

Of the 24 control dogs, seven (29 per cent) died of ventricular fibrillation during or immediately after the left anterior descending coronary branch ligation; and 9 additional dogs (37 per cent) died within twenty-four hours after ligation. Five of these dogs had pneumonic patches, one probably died of the effect of cyanide and the rest of cardiac failure. Seven (29 per cent) survived one week and were then sacrificed. Elim-

inating from this series those dogs which died from pneumonia leaves a one-week survival rate of 39 per cent.

The immediate fall in average cardiac output after coronary ligation was of about the same magnitude in both the ganglionectomized (Tables I and II) and control dogs\* (approximately 50 per cent of preligation level). After twenty-four hours the average cardiac output approximated preligation values in the control group whereas there was only a small rise in the ganglionectomized dogs (Fig. 1). After one week, the ganglionectomized dogs exhibited a further rise in cardiac output

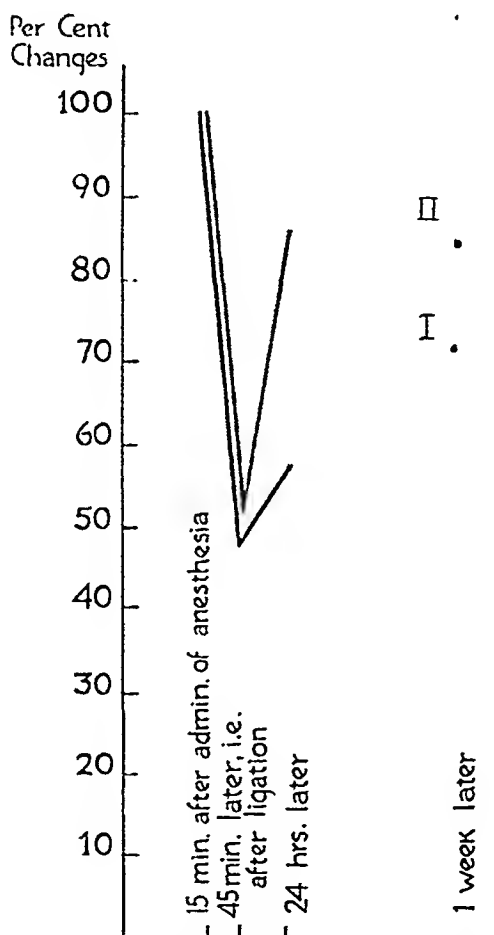


Fig. 1.—Average per cent of changes in cardiac output per square meter of surface area after occlusion of the left anterior descending coronary branch.

I. Ganglionectomized dogs; II. Dogs with ganglia intact. This curve represents average values from a group previously reported<sup>3</sup> plus experiments performed simultaneously with the ganglionectomized dogs.

to 72 per cent of the preligation values, and the control dogs showed relatively little change.

In both groups of animals (Table II), coronary ligation was followed by an immediate moderate fall in arterial blood pressure which reached 62 per cent of the preligation level at the end of twenty-four hours. One week after the coronary ligation there was an appreciable rise in the ganglionectomized group, but the blood pressure in the control group

\*For detailed data on hemodynamic changes in control dogs, see reference 3.





TABLE I—CONT'D

|    |   |   |                               |                              |                          |                          |                              |                              |                              |                        |                        |         |             |
|----|---|---|-------------------------------|------------------------------|--------------------------|--------------------------|------------------------------|------------------------------|------------------------------|------------------------|------------------------|---------|-------------|
| 29 | ♀ | Preligation<br>Postligation<br>Retested | 1/26/37                       | 9.2<br>9.2<br>8.6            | 92<br>72<br>140          | 90<br>71<br>85           | 6.35<br>6.28<br>5.72         | 2882<br>2300<br>3158         | 2098<br>1933<br>2120         | 115<br>65<br>65        | 13<br>35<br>15         | 2/ 1/37 | 4 × 3.5 cm. |
| 30 | ♀ | Preligation<br>Postligation<br>Retested | 1/27/37<br>1/28/37<br>1/29/37 | 16.3<br>16.3<br>15.7         | 108<br>124<br>112        | 148<br>165<br>146        | 1.79<br>6.48<br>7.42         | 11370<br>3525<br>2803        | 2546<br>2610<br>2598         | 130<br>112<br>85       | 10.5<br>22.5<br>35.0   | 2/ 1/37 | 5 × 4 cm.   |
| 44 | ♂ | Preligation<br>Postligation<br>Retested | 1/29/37<br>1/30/37<br>2/ 5/37 | 18.2<br>18.2<br>17.8<br>17.5 | 120<br>128<br>120<br>112 | 149<br>130<br>134<br>135 | 3.15<br>6.47<br>6.80<br>5.05 | 6124<br>2598<br>2585<br>3532 | 2307<br>2108<br>2096<br>—    | 128<br>98<br>70<br>75  | 9<br>20.5<br>24<br>18  | 2/ 5/37 | 3 × 2 cm.   |
| 64 | ♂ | Preligation<br>Postligation<br>Retested | 2/ 2/37<br>2/ 3/37<br>2/10/37 | 10.0<br>10.0<br>9.6<br>10.3  | 100<br>84<br>84<br>104   | 87<br>76<br>94<br>99     | 3.59<br>4.89<br>6.43<br>4.15 | 4648<br>2980<br>2883<br>4480 | 2442<br>2198<br>2980<br>2548 | 105<br>65<br>65<br>112 | 14<br>37<br>25<br>10.5 | 2/10/37 | 5 × 3.5 cm. |
| 82 | ♂ | Preligation<br>Postligation             | 2/ 3/37                       | 9.3<br>9.3                   | 100<br>100               | 169<br>154               | 2.25<br>6.70                 | 15160<br>4030                | —<br>—                       | 105<br>90              | 11<br>—                | 2/ 3/37 | No infarct  |
| 81 | ♂ | Preligation<br>Postligation<br>Retested | 2/ 9/37<br>2/10/37            | 13.6<br>13.6<br>12.9         | 102<br>86<br>108         | 111<br>103<br>115        | 2.48<br>4.00<br>6.26         | 7000<br>4020<br>2988         | 1796<br>1736<br>1473         | 158<br>105<br>90       | 9<br>12<br>indefinite  | 2/13/37 | 4.5 × 4 cm. |
| 96 | ♀ | Preligation<br>Postligation             | 2/15/37                       | 11.0<br>11.0                 | 124<br>104               | 97<br>88                 | 2.06<br>4.15                 | 8483<br>3820                 | 1936<br>1494                 | 85<br>88               | 12<br>19               | 2/16/37 | 4 × 3 cm.   |

remained at approximately the same level as that at the end of the twenty-four-hour postligation period.

Following coronary occlusion (Table II) the cyanide circulation time was immediately increased in both groups. The delay was somewhat greater in the ganglionectomized animals. The changes persisted for at least twenty-four hours and reached almost normal values at the end of one week.

The circulating blood volume (Table II) showed an insignificant drop in both groups, with rapid restoration to preligation levels. The hemoglobin determination presented no significant deviations from the preligation levels in either group. The temperature showed a slight drop in both groups after ligation. The pulse became irregular im-

TABLE II

COMPARISON OF THE AVERAGE HEMODYNAMIC CHANGES DUE TO CORONARY LIGATION IN STELLATE GANGLIONECTOMIZED DOGS AND IN DOGS WITH INTACT STELLATE GANGLIA

|                           | PRELIGATION | POST-LIGATION | 24 HR. LATER | 1 WK. LATER |
|---------------------------|-------------|---------------|--------------|-------------|
| Cardiac output*           |             |               |              |             |
| Ganglionectomized         | 100         | 48.4          | 57.2         | 72.1        |
| Controls                  | 100         | 51.9          | 55.8         | 84.1        |
| Blood volume*             |             |               |              |             |
| Ganglionectomized         | 100         | 88            | 92           | 101         |
| Controls                  | 100         | 94            | 102          | 102         |
| Arterial blood pressure†  |             |               |              |             |
| Ganglionectomized         | 100         | 74            | 62           | 79          |
| Controls                  | 100         | 84            | 62           | 65          |
| Cyanide circulation time† |             |               |              |             |
| Ganglionectomized         | 100         | 186           | 195          | 129         |
| Controls                  | 100         | 166           | 169          | 123         |

\*Average per cent changes per square meter of surface area.

†Average per cent changes.

mediately after the ligation in most of the controls but in none of the ganglionectomized animals. Some of the latter showed an irregular pulse only after twenty-four hours.

In judging the extent of infarction, it should be borne in mind that it is unsafe to draw conclusions from the surface measurements alone. Injection of infarcted hearts with barium sulfate gelatine under standard conditions with subsequent radiography and study of serial cross-sections discloses that infarcts which show a small surface area may at times present extensive involvement of the interventricular septum. Furthermore, in appraising the comparative extent of the infarction, differences in the weight of the dogs must also be considered. Based on these criteria there did not appear to be an appreciable difference in the size of the infarcts between the ganglionectomized dogs and those with intact ganglia.

## DISCUSSION

Our observations as to the immediate onset of ventricular fibrillation, as well as the mortality rate within the first twenty-four hours after coronary branch ligation, confirm the findings of Cox and Robertson in that these appear to be significantly lower in the ganglionectomized animals. Furthermore, survival one week after vascular ligation appeared to be higher in the ganglionectomized dogs. Unfortunately, the total number of animals studied was too small to warrant definite conclusions as to ultimate survival rate.

With the reservations mentioned above, there did not appear to be an appreciable difference between the two groups as regards the size of the infarct. It is noteworthy in this connection that Cox and Robertson studied the size of the infarcts several months after coronary occlusion. Because of the considerable variability in the rate of cicatrization of infarcts we feel that their results in this connection cannot be accepted without reserve, especially since no injection studies were made.

The only significant hemodynamic changes which followed coronary occlusion were decrease in cardiac output, delay in cyanide circulation time, and fall in mean arterial blood pressure. The immediate changes were of about the same degree in both groups of animals. Within a week following the vascular occlusion the cyanide circulation time had almost reached preligation levels in both groups of animals. The controls showed a considerable return to normal in cardiac output within twenty-four hours after coronary ligation, whereas the ganglionectomized group showed a somewhat slower return to normal values. On the other hand, the ganglionectomized group showed a somewhat better restoration of mean arterial blood pressure at the end of one week. Although the number of animals which survived one week was small, it would appear that, with the possible exception of the mean arterial blood pressure, within one week after vascular ligation these hemodynamic functions were not significantly different in both groups of animals.

## SUMMARY

Studies on mortality rate, cardiac output, pulse rate, arterial blood pressure, cyanide circulation time, and blood volume as well as measurement of the size of the infarcts following occlusion of the left anterior descending coronary branch were carried out in dogs with stellate ganglia intact and in stellate ganglionectomized dogs. These studies were done immediately before vascular ligation, immediately after ligation, twenty-four hours, and one week after ligation. Following occlusion of the left anterior descending coronary branch there occurred in both groups of animals a fall in cardiac output, delay in cyanide circulation time, and fall in blood pressure. It is shown that these hemodynamic changes tend to return to normal values after one week.

The other hemodynamic functions studied showed no appreciable changes. The incidence of ventricular fibrillation and the immediate mortality rate was lower in the ganglionectomized dogs. The size of the infarcts was not appreciably different from the controls.

## REFERENCES

1. Cox, W. V., and Robertson, H. F.: The Effect of Stellate Ganglionectomy on the Cardiac Function of Intact Dogs, *AM. HEART J.* 12: 285, 1936.
2. Gross, Louis, Mendlowitz, M., and Schauer, G.: Hemodynamics Following Experimental Coronary Occlusion in Dogs, *Proc. Soc. Exper. Biol. & Med.* 35: 446, 1936.
3. Gross, Louis, Mendlowitz, M., and Schauer, G.: Hemodynamic Studies in Experimental Coronary Occlusion. I. Open Chest Experiments, *AM. HEART J.* 13: 647, 1937.
4. Mendlowitz, M., Gross, Louis, and Schauer, G.: Hemodynamic Studies in Experimental Coronary Occlusion. II. Closed Chest Experiments, *AM. HEART J.* 13: 664, 1937.
5. Mendlowitz, M., Schauer, G., and Gross, Louis: Hemodynamic Studies in Experimental Coronary Occlusion. III. Denervated Heart Experiment, *AM. HEART J.* 14: 21, 1937.
6. Gross, Louis: The Blood Supply to the Heart, New York, 1921, Paul B. Hoeber.
7. Gross, Louis, and Kugel, M. A.: The Arterial Blood Vascular Distribution to the Left and Right Ventricles of the Human Heart, *AM. HEART J.* 9: 165, 1933.
8. Gross, Louis, Blum, Lester, and Silverman, Gertrude: Experimental Attempts to Increase the Blood Supply to the Dog's Heart by Means of Coronary Sinus Occlusion, *J. Exper. Med.* 65: 91, 1937.

ELECTROCARDIOGRAPHIC CHANGES IN THE DOG FOLLOW-  
ING SUDDEN OCCLUSION OF THE LEFT ANTERIOR  
DESCENDING CORONARY BRANCH UNDER VARIOUS  
EXPERIMENTAL CONDITIONS\*

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MANY reports have appeared on the electrocardiographic changes following ligation of the anterior descending branch of the left coronary artery in dogs. The authors, however, are not agreed on the characteristic findings. Following left anterior descending coronary branch ligation on 11 dogs, Smith<sup>1</sup> found that the T-waves were first exaggerated, became negative in twenty-four hours, gradually came back to normal and then remained isoelectric or negative. Otto<sup>2</sup> studied only Lead II following this procedure. He described an abnormally depressed R-T segment and a high peak of the T-waves. Feil, Katz, Moore, and Scott<sup>3</sup> found no changes in the R-T segment of the electrocardiogram following ligation of the left anterior descending coronary branch unless the blood supply to the heart was impaired by occluding the inferior vena cava for five minutes. Barnes and Mann<sup>4</sup> observed that occlusion of branches of the left coronary artery produced an elevation of R-T<sub>1</sub>, depression of S-T<sub>3</sub>, and marked negativity of T<sub>1</sub>. Kountz and Hammouda<sup>5</sup> produced occlusion of the anterior descending branch of the left coronary artery in heart-lung preparations in dogs. Their most frequent findings were elevation of the R-T segment in all three leads, and an occasional depression of R-T<sub>1</sub> and S-T<sub>3</sub>. The T-waves were usually inverted in all three leads but occasionally inverted in Lead I and upright in Lead III. Harris, Sutherland, Ramsey, and Gaiser<sup>6</sup> found no constant changes following left anterior descending branch occlusion in 17 dogs. R-T<sub>1</sub> elevations were noted only four times. In an admirably painstaking and thorough study of serial electrocardiograms in 51 dogs taken before and after ligation of the left anterior descending branch, Harris and Hussey<sup>7</sup> concluded that this procedure is followed by regular changes, namely, early R-T deviation of the T<sub>1</sub> type (78 per cent of cases), increased amplitude of the T-waves and sharp negativity of the T-waves, particularly in Lead I. Disturbances in rhythm followed a definite pattern progressing through the following stages: (1) ectopic beats singly or from multiple foci; (2) paroxysms

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\*Aided by grants from the Lucius N. Littauer and Walter W. Naumburg Funds,

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of ectopic ventricular tachycardia; (3) ventricular flutter; (4) ventricular fibrillation. In some dogs which survived these changes, this sequence was reversed. Harris and Hussey noted further the extreme variability of the normal T-waves in dogs, sometimes finding negative T-waves even in all three leads in the control tracings. This confirms the observations of Katz and his associates<sup>9</sup> who believed these changes were due to the mobility of the heart in the dog's chest.

In a series of experimental studies on partial and complete coronary sinus obturation followed by sudden occlusion of the left anterior descending coronary branch carried out by Gross and collaborators,<sup>7-12</sup> an opportunity was afforded to determine the electrocardiographic changes due to a variety of experimental procedures. Those following coronary sinus obturation have already been reported elsewhere.<sup>10</sup> The present report deals with the electrocardiographic findings in the following groups of animals:

- A. Thirty-four dogs in which only left anterior descending coronary branch occlusion was performed:
  1. By dissection and ligation of the left anterior descending coronary branch in the open chest (10 dogs).
  2. By ligation without dissection of the left anterior descending coronary branch in the open chest (15 dogs).
  3. By the double carrick-bend knot method<sup>12</sup> in the closed chest (9 dogs).
- B. Thirty-five dogs in which left anterior descending coronary branch occlusion was performed in the open chest by ligation, after recovery from an initial preparatory operation consisting of:
  1. Complete obturation of the coronary sinus (7 dogs).
  2. Partial obturation of the coronary sinus (21 dogs).
  3. Manipulation of the coronary sinus ostium (7 dogs).
- C. Twenty-four control dogs in which the left anterior descending coronary branch was either:
  1. Dissected without subsequent occlusion (7 dogs), or
  2. Dissected and loosely surrounded by a double carrick-bend knot (17 dogs).

All operative procedures, including vascular occlusion by the double carrick-bend knot method, were carried out under intravenous nembutal anesthesia. The dissection or ligation of the left anterior descending coronary branch was performed approximately 2 cm. below the ostium of the left coronary artery. The observations made during the course of these experiments will be discussed under two headings, viz.:

I. Summary of the electrocardiographic changes following left anterior descending branch occlusion under the conditions listed in Groups A and B; and the findings in Group C, in which the coronary branch was manipulated but no occlusion was produced.

II. Differences noted in the several groups and subgroups.

I. SUMMARY OF ELECTROCARDIOGRAPHIC CHANGES FOLLOWING SUDDEN COMPLETE OCCLUSION OF THE LEFT ANTERIOR DESCENDING CORONARY BRANCH UNDER THE CONDITIONS LISTED IN GROUPS A, B, AND C

Sudden complete occlusion of this vessel was obtained in 69 dogs. Electrocardiograms were taken pre-operatively, during anesthesia with the pericardium opened, after manipulation or dissection of the left anterior descending branch, immediately after occluding the vessel, and at various intervals (one to three days) after the operation until the dog died or was sacrificed. Because of the low voltage in Lead I in dogs, it was found advantageous to take records of this lead by using a standardization twice that of the conventional one (1 millivolt equals 2 cm.); as well as the conventional Lead I.

*R-T Changes*

The electrocardiographic findings most characteristic in dogs after ligation of the left anterior descending branch, appeared in the R-T and S-T segments (Table I). In most cases the changes consisted of R-T<sub>1</sub>

TABLE I

PER CENT OF DOGS SHOWING R-T<sub>1</sub> ELEVATION AND S-T<sub>2</sub> AND S-T<sub>3</sub> DEPRESSION FOLLOWING THE VARIOUS PROCEDURES LISTED

| PROCEDURE  |   | R-T <sub>1</sub><br>ELEVATION | S-T <sub>2</sub><br>DEPRESSION | S-T <sub>3</sub><br>DEPRESSION | R-T <sub>1</sub> ELEVATION<br>OR S-T <sub>3</sub><br>DEPRESSION |
|--|---|-------------------------------|--------------------------------|--------------------------------|---|
| SUDDEN COMPLETE LEFT ANTERIOR<br>DESCENDING BRANCH OCCLUSION     | A. Unprepared dogs*   |                               |                                |                                |   |
|  | 1. Dissection and ligation (10 dogs)                                | 70                            | 40                             | 60                             | 80  |
|  | 2. Ligation (15 dogs)   | 46                            | 53                             | 53                             | 80  |
|  | 3. Double carrick-bend knot ligation (9 dogs)                       | 88                            | 33                             | 54                             | 88  |
|  | Total unprepared dogs (34 dogs)                                     | 65                            | 44                             | 53                             | 82  |
|  | B. Prepared dogs†   |                               |                                |                                |   |
|  | 1. Complete coronary sinus (7 dogs) occlusion                       | 86                            | 57                             | 57                             | 86  |
|  | 2. Partial coronary sinus (21 dogs) occlusion                       | 81                            | 61                             | 71                             | 95  |
|  | 3. Manipulation of coronary (7 dogs) sinus ostium without occlusion | 71                            | 44                             | 44                             | 85  |
|  | Total prepared dogs (35 dogs)                                       | 80                            | 57                             | 62                             | 91  |
|  | A. + B. TOTAL PREPARED AND UNPREPARED DOGS (69 dogs)                | 72                            | 50                             | 58                             | 90  |
| CONTROL SERIES<br>(No left anterior descending branch occlusion) | C.  |                               |                                |                                |   |
|  | 1. Dissection only (7 dogs)   | 0                             | 14                             | 14                             | 14  |
|  | 2. Loose double-carrick-bend knot (17 dogs)                         | 0                             | 11                             | 11                             | 11  |
|  | Total controls (24 dogs)  | 0                             | 12                             | 12                             | 12  |

\*No preliminary coronary sinus occlusion.

†Ligation of the left anterior descending coronary branch was performed in these animals after recovery from the procedures listed.



elevations or S-T<sub>2</sub> and S-T<sub>3</sub> depressions. One or both of these changes occurred in 90 per cent of the ligated dogs, usually within fifteen minutes after the occlusion, and tended to disappear within or shortly after twenty-four hours. The R-T<sub>1</sub> segment was elevated in 72 per cent of dogs with occlusion, whereas this never occurred in the control dogs. S-T<sub>3</sub> depression was found in 58 per cent of the ligated animals and in only 12 per cent of the control dogs. As a rule, when the deviations were present in the control groups, they were not as marked as in those with ligation.

### *Rhythm Changes*

On rare occasions, single and infrequent ventricular premature beats followed the administration of anesthesia. After left anterior descending branch occlusions, these premature contractions became very much more frequent. They apparently originated from the left or right ventricles and from one or more foci in each ventricle. They occurred either singly or in short or long paroxysms, and merged imperceptibly with what was interpreted as ventricular extrasystolic tachycardia, or ventricular anarchy. In the latter instances, P-waves were usually observed and were of regular rhythm. This type of ventricular rhythm was noted only once in control dogs and ten times in dogs following coronary occlusion. There is no doubt but that abnormalities in rhythm occur very much more frequently than noted by us electrocardiographically. We have observed them before electrocardiograms could be taken, the hearts resuming normal rhythm or, on the other hand, changing to ventricular fibrillation. The changes were very rapid and sometimes transient. In one instance, immediately after occluding the left anterior descending branch from outside the chest (double-carriek-bend knot), Lead I showed typical R-T<sub>1</sub> elevation with regular sinus rhythm, while Lead II showed ventricular fibrillation. It is estimated that these changes occurred in less than five seconds. No instance of auricular premature contraction or auricular fibrillation was observed.

### *Other Changes*

The QRS voltage did not vary uniformly in either the control or ligated dogs. Opening the chest and instituting artificial respiration produced QRS voltage variations synchronous with the respiratory phases. Alternation of the QRS complex was noted only once in the control series. This dog was apparently in surgical shock. Slurring and notching occurred as frequently in control dogs as in the ligated ones. When the rhythm was regular, the duration of the QRS deflection varied within normal limits and inversely with the heart rate.

Because of the normal variation of T-waves in dogs occurring from day to day, only those records taken before and immediately after a given procedure were compared. The normally low or iso-electric T<sub>1</sub>

tended to become inverted though still low in amplitude after left anterior descending branch ligation.  $T_2$  and  $T_3$ , on the other hand, tended to become more positive, i.e., the upright T-wave became greater in amplitude and the inverted T-wave became smaller in amplitude after such ligation. One cannot say with certainty whether these changes are characteristic of left anterior descending branch occlusion in dogs. They occurred in 21 per cent of the control animals and in 67 per cent of the animals in which the coronary branch had been occluded. Very similar changes were reported by Gross, Silverman, and Master<sup>10</sup> following coronary sinus occlusion in dogs. Right ventricular preponderance was observed in five ligated dogs but in none of the controls.

## II. DIFFERENCES IN THE ELECTROCARDIOGRAPHIC FINDINGS DUE TO THE VARIOUS PROCEDURES LISTED ABOVE

In order to observe whether occlusion of the left anterior descending branch within a closed chest wall was followed by changes which differed from such occlusion performed in the usual manner (open chest), the double carrick-bend procedure was employed. This was performed by placing two loose ligatures around the coronary artery and leading the ends through the pericardium and chest wall.<sup>11</sup> The ligatures were so arranged that tension applied to them after the chest wall was completely closed and healed produced an immediate and complete occlusion of the coronary branch. This occlusion was performed in the anesthetized animal about one week after recovery from the initial operation. The somewhat greater frequency of R- $T_1$  elevations following this procedure than those following ligation or ligation plus dissection in the open chest (Table I), may be due to improved technique.

R- $T_1$  elevations appear to be somewhat more frequent in the groups in which previous coronary sinus obturation preceded coronary artery occlusion (Table I). These changes may possibly be attributable to congestion of the heart producing axis deviation, or to added damage to the myocardium due to congestion, or to both.

Table II lists the combinations of R- $T_1$ , S- $T_2$  and S- $T_3$  deviations following various procedures. The groups are too small to warrant definite conclusions but are listed as a matter of record.

## SUMMARY AND CONCLUSIONS

The reported groups of experiments confirm the findings of Harris and Hussey.<sup>7</sup>

Sudden complete occlusion of the anterior descending branch of the left coronary artery in the dog is followed characteristically by an upward deviation of the R-T segment of the electrocardiogram in Lead I, and a downward deviation from the iso-electric level in Leads II and III. Either or both of these changes were noted in 90 per cent of ligated dogs as compared with 12 per cent in the control dogs.

TABLE II  
PER CENT OF DOGS SHOWING CERTAIN COMBINATIONS OF R-T<sub>1</sub>, S-T<sub>1</sub>, AND S-T<sub>2</sub> DEVIATIONS DUE TO THE VARIOUS PROCEDURES LISTED

| SUDDEN COMPLETE LEFT ANTERIOR DESCENDING BRANCH OCCLUSION |                  |                  |                                       |                    |                                   | CONTROL SERIES   |                 |
|---|------------------|------------------|---------------------------------------|--------------------|-----------------------------------|--|-----------------|
| Unprepared dogs*  |                  |                  |                                       |                    |                                   | (No left anterior descending branch occlusion)                   |                 |
| R-T <sub>1</sub>  | S-T <sub>1</sub> | S-T <sub>2</sub> | Double carrick-bend ligation (9 dogs) | Ligation (15 dogs) | Dissection and ligation (10 dogs) | Total (34 dogs)  | Total (24 dogs) |
| Prepared dogs†  |                  |                  |                                       |                    |                                   | Manipulation of coronary sinus ostium without occlusion (7 dogs) |                 |
|   |                  |                  |                                       |                    |                                   | Complete coronary sinus occlusion (7 dogs)                       | Total (35 dogs) |
|   |                  |                  |                                       |                    |                                   | Partial coronary sinus occlusion (21 dogs)                       | Total (35 dogs) |
| †   | †                | †                | 34                                    | 20                 | 30                                | 57   | 48              |
| †   | 0                | 0                | 22                                    | 20                 | 20                                | 29   | 28              |
| 0   | †                | †                | 11                                    | 20                 | 10                                | 14   | 8               |
| 0   | 0                | 0                | 11                                    | 13                 | 20                                | 14   | 8               |
| 0   | 0                | †                | 22                                    | 10                 | 10                                | 5  | 3               |
| †   | †                | †                | 11                                    | 13                 | 10                                | 5  | 3               |
| 0   | †                | †                | 34                                    | 34                 | 10                                | 14   | 4               |
| †   | †                | 0                |                                       |                    | 10                                | 14   | 4               |

\*No preliminary coronary sinus occlusion.

†Ligation of the left anterior descending coronary branch was performed in these animals after recovery from the procedures listed.

These changes are comparable to electrocardiographic findings in the human being following anterior infarctions. Unlike the latter, however, the R-T segment tended to return to normal very early. This may be due to the fact that the dogs had no coronary sclerosis or myocardial fibrosis and were therefore capable of compensating more rapidly for the sudden change in the myocardial physiological functions.

The characteristic cove-plane inversion of the T-waves in humans was noted in normal dog electrocardiograms. However, comparing records before and after left anterior descending coronary branch occlusion showed a tendency for  $T_1$  to become more inverted and for  $T_2$  and  $T_3$  to become more upright.

Rhythm abnormalities ranging from single ectopic beats to ventricular fibrillation were noted with great frequency following sudden complete coronary occlusion.

In an attempt to increase the blood supply to the heart and thus diminish the incidence or size of infarction, partial and complete coronary sinus obturation was performed in a number of the dogs prior to the coronary branch occlusion. In the comparatively few animals in which electrocardiographic studies were made there was found a slightly greater incidence of changes considered characteristic of coronary occlusion, but there was no definite correlation between the size of infarct and the degree of electrocardiographic changes.

Other differences in the electrocardiographic findings due to various procedures are discussed and listed.

#### REFERENCES

1. Smith, Fred M.: The Ligation of Coronary Arteries With Electrocardiographic Study, *Arch. Int. Med.* 22: 8, 1918.
2. Otto, Harold L.: The Effect of Obstruction of Coronary Arteries Upon the T-Wave of the Electrocardiograph, *AM. HEART J.* 4: 346, 1929.
3. Feil, H. S., Katz, L. N., Moore, R. D., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischemia, *AM. HEART J.* 6: 522, 1931.
4. Barnes, Arlie R., and Mann, Frank C.: Electrocardiographic Changes Following Ligation of the Coronary Arteries of the Dog, *AM. HEART J.* 7: 477, 1932.
5. Kountz, W. B., and Hammouda, M.: Effects of Asphyxia and of Anoxemia on the Electrocardiogram, *AM. HEART J.* 8: 259, 1932.
6. Harris, B. R., Sutherland, F. A., Ramsey, E. N., and Gaiser, D. W.: Observations on Coronary Occlusion. II. Electrocardiographic Changes, *Proc. Soc. Exper. Biol. & Med.* 31: 222, 1933.
7. Harris, B. R., and Hussey, R.: The Electrocardiographic Changes Following Coronary Artery Ligation in Dogs, *AM. HEART J.* 12: 724, 1936.
8. Katz, L. N., Soskin, S., and Frisch, R.: Variations in Contour of the Records Found in Serial Electrocardiograms of the Dog, *Proc. Soc. Exper. Biol. & Med.* 32: 208, 1934.
9. Gross, Louis, and Blum, Lester: Effect of Coronary Artery Occlusion on Dog's Heart With Total Coronary Sinus Ligation, *Proc. Soc. Exper. Biol. & Med.* 32: 1578, 1935.
10. Gross, Louis, Silverman, G., and Master, A. M.: Electrocardiographic Changes Following Coronary Sinus Occlusion in the Dog's Heart, *AM. HEART J.* 11: 734, 1936.
11. Mendlowitz, M., Schauer, G., and Gross, Louis: Hemodynamic Studies in Experimental Coronary Occlusion. II. Closed Chest Experiments, *AM. HEART J.* 13: 664, 1937.
12. Gross, Louis, Blum, L., and Silverman, G.: Experimental Attempts to Increase the Blood Supply to the Dog's Heart by Means of Coronary Sinus Occlusion, *J. Exper. Med.* 65: 91, 1937.

# INFARCTION OF THE HEART

## A MORPHOLOGICAL AND CLINICAL APPRAISAL OF THREE HUNDRED CASES\*

### PART I. PREDISPOSING AND PRECIPITATING CONDITIONS

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THE basis of this study consists of 300 autopsied cases selected from 9,626 consecutive protocols in the department of pathology of this hospital for the years 1906 through 1936.† Selection was determined by the finding of (1) typical morphological infarction with or without complete obstruction of the nutrient artery; (2) well-defined gross scar 2.5 cm. or more in diameter, with or without complete occlusion of the artery; (3) embolic or other apparently sudden occlusion without gross damage, but with early microscopic change. No cases are included in which death came at once; all survived at least one hour. At least 11 cases of complete occlusion (2 syphilitic, 1 embolic and 8 arteriosclerotic) were discarded because evidence of resultant damage was equivocal. Cases incompletely or vaguely described as myelomalacia cordia, fatty degeneration, myocarditis or senile degeneration were omitted.

After the cases were selected the clinical records were examined. A few clinical records were incomplete so that data on some of the factors analyzed were lacking. In the text and tables the percentages are given on the basis of the number of cases in which the factors in question were ascertained, rather than on the whole group.

During the thirty-one-year period covered by the study there were 697,099 admissions to the hospital, 58,081 deaths and 9,626 autopsies, including the 300 cases presented. Since post-mortem examinations in this country average 1 or 2 per cent of all deaths, in contrast to 17 per cent for the group here, the possible statistical error is considerable in such a study as this. The percentage of autopsies obtained is largely influenced by interest of the permission seeker, which in recent years has been great in cases of suspected coronary thrombosis. Many other factors also preclude accuracy in drawing statistical conclusions.

#### ARTERIOSCLEROSIS AND MYOCARDIAL INFARCTION

The overwhelming majority of all cases of myocardial infarction are due to coronary arteriosclerotic changes, which may or may not result

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†These have been compiled under the direction of Dr. Frank B. Mallory and Dr. Frederic Parker, Jr., and include gross and microscopic studies by the junior and senior pathologists.

in thrombosis. The term coronary occlusion has become tantamount to cardiac infarction, a synonymy not altogether justified. Arteriosclerosis, and especially atherosclerosis, is usually associated with old age, though an early variety has been reported in infants<sup>19</sup> and in young adults.<sup>47, 20</sup> In a combined necropsy and experimental study Leary has called attention to two fundamentally different types of arterial change evoked by the pathogenesis in old and in young animals or human beings.<sup>23, 24</sup> The young react with a fibrotic lesion which predominates over the lipid deposits. Later subendothelial necrosis extends to the endothelium, and finally narrowing and thrombosis result. In the older group the lesion is characterized by the accumulation of lipid cells with but minimal fibrous tissue support, finally causing thrombosis by rupture of the atheromatous abscess.

The work on experimentally produced arterial disease has been immense.<sup>10</sup> It seems that sclerosis may be produced by injections of epinephrine or of bacteria, or by high protein diets.<sup>37</sup> Atherosclerosis can be induced in rabbits by high cholesterol feedings. There are contributory factors of stress, toxicity, and inflammatory localization. Leary believes that when hypercholesteremia occurs in conjunction with (or perhaps as a manifestation of) a disturbed cholesterol metabolism, atherosclerosis will occur. He cites the experience of Joslin and Rabinowich, who have noted a decrease in juvenile arterial lesions since the high fat diet was abandoned in treatment of diabetes. Freyberg and his coworkers<sup>14</sup> think lack of regulation of the diabetic state rather than a diet high in fat causes hypercholesteremia. Levy<sup>30</sup> has called attention to an unusually high incidence of coronary sclerosis in glomerulonephritis and hypothyroidism as well as diabetes mellitus.

In this series generalized arteriosclerosis as manifested by the necropsy evidence, particularly of a diseased aorta, or by the clinical findings of thickened, tortuous, or calcified vessels, or arteriosclerotic changes in the retinal arteries, was present in 261 of 272 in whom data were found. In 8 it was extreme, in 18 slight or minimal, and in the rest it was moderate. Coronary occlusion is usually associated with coronary sclerosis, but generalized arteriosclerosis is not necessarily present. Peripheral sclerosis is often of the medial type,<sup>3</sup> whereas in the coronary arteries subintimal change is important. The occurrence of the various types of arteriosclerosis is found in Table I. The preponderance of cases with coronary arterial disease in this series shows its importance in thrombosis and designates it as the prepotent etiological factor.

#### ADDITIONAL EVIDENCE OF ARTERIAL DISEASE

*Cerebral Vascular Disease.*—Many other conditions have their origin in arterial changes similar to those occurring in the arteries to the heart,

giving further evidence of disseminated arterial disease. There were 11 instances of hemiplegia which definitely preceded cardiac infarction, and an additional 10 in which it was probable that cerebral injury depended on a local fault but in which embolus could not be ruled out.

*Peripheral Arterial Disease.*—Nine individuals had suffered from either classical intermittent claudication or disability from pain upon walking. Post-mortem examinations of the leg arteries were not made so it is not certain whether arteriosclerotic or inflammatory lesions were present. Lemann<sup>25</sup> was one of the first to note intermittent claudication and coronary thrombosis in the same individual.<sup>25, 42</sup> Four cases of this series were admitted with arteriosclerotic gangrene, and two with diabetic gangrene not embolic in origin. Two individuals had had amputations for gangrene prior to admission. There was one case of severe frostbite.

TABLE I  
THE OCCURRENCE OF VARIOUS TYPES OF ARTERIOSCLEROSIS

| TYPE   | INCIDENCE  | PER CENT |
|--|------------|----------|
| Generalized arteriosclerosis                   | 261 of 272 | 96.0     |
| Coronary arteriosclerosis                      | 269 of 274 | 98.2     |
| Peripheral arteriosclerosis (without coronary) | 3          |          |
| Coronary arteriosclerosis (without peripheral) | 8          |          |
| No arteriosclerosis                            | 2          |          |

*Angina Pectoris.*—In this series a reliable history regarding angina was found in 125 records. It had been present in 29 individuals in its typical form, and in 13 there was pain with an atypical distribution or radiation before the initial infarction. This incidence of only 33.6 per cent is lower than Levine's,<sup>26</sup> but the discrepancy may be partly dependent on the class of patients and language difficulties encountered in this hospital, or on the likelihood that previously occurring anginal pain, especially if mild, might well have been forgotten in the more urgent agony of acute infarction.

*Arterial Hypertension.*—The importance of hypertension in angina pectoris and cardiac infarction has been appreciated for a long time. It can be considered etiological only so far as it is related to coronary artery disease. While Wearn<sup>44</sup> found hypertension in only one of 19 cases, Parkinson and Bedford<sup>38</sup> found it in 49 per cent of 100 cases, Conner and Holt<sup>9</sup> report it in 34 per cent of 287 cases, White and Bland<sup>45</sup> in 25 per cent of 200. Levine<sup>26</sup> found preexisting hypertension in 40 per cent of 145 cases, with a disproportionate number of females. The finding of high arterial pressure in this series is tabulated in Table II. Taking those with known previous hypertension and those with systolic tension over 160 or diastolic over 100, 49.3 per cent of the 270 had elevated blood pressure. Thirty-one per cent were female, 69 per

cent male, the same sex ratio as the entire series. All cases with arterial hypertension showed coronary disease except one case of syphilitic narrowing and occlusion of the coronary mouth. On the other hand, numerous cases had arteriosclerosis without hypertension. The percentage of hypertensives and nonhypertensives having initial infarction in different decades is shown in Fig. 1. Of the women with history of hypertension, 41.4 per cent were obese and only 24 per cent of the men were obese, indicating relatively more women than men with obesity in the hypertensive group.

## SEX

In every reported statistical work there has been a notable preponderance of males: Wearn,<sup>44</sup> 10 to 9, Parkinson and Bedford,<sup>38</sup> 165 to

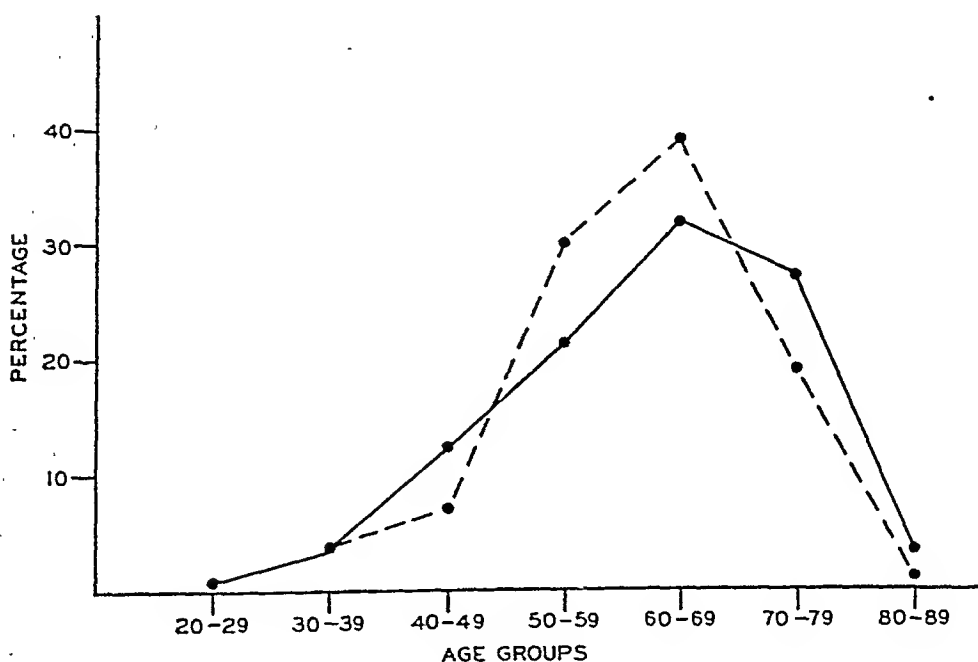


Fig. 1.—Age at initial infarction: Comparison of age at onset among 100 known patients with hypertension (broken line) and 122 cases where hypertension was not demonstrated (solid line).

18, Levine,<sup>26</sup> 111 to 34, Conner and Holt,<sup>9</sup> 244 to 43, White and Bland,<sup>45</sup> 167 to 33, Appelbaum and Nicolson,<sup>1</sup> 125 to 25, Wilhelmy and Helwig,<sup>48</sup> 72 to 16, Goldsmith and Willius,<sup>15</sup> 272 to 28. In these reports taken together the females constituted only 15 per cent of all cases. There were 209 males to 91 females in our group (Table III), or 30.3 per cent females. Thus there was twice the proportion of females in this series as the average in the others. Hypertension was represented proportionally in the two sexes. Though most of the patients in this report died within the last ten years, it is interesting that the sex ratio for the 18 cases in the first ten years was two males to one female, essentially the same as for the total series. There is no indication that the percentage of females dying with myocardial infarction is increasing relative to males, though there are not enough cases in the



TABLE II  
PREEXISTING VASCULAR DISEASE AND RELATED STATES

|   | INCIDENCE  | PER CENT |
|---|------------|----------|
| Coronary arteriosclerosis                             | 269 of 274 | 98.2     |
| Generalized arteriosclerosis                          | 261 of 272 | 96.0     |
| Hypertension (history and/or elevated blood pressure) | 133 of 279 | 49.3     |
| History positive                                      | 66 of 91   | 72.5     |
| History unknown; blood pressure above 160/100         | 67         |          |
| Angina pectoris                                       |            |          |
| Typical   | 29         | >        |
| Atypical  | 13         |          |
| Diabetes mellitus                                     | 42 of 125  | 33.6     |
| Preexisting hemiplegia                                | 19 of 100  | 17.4     |
| Definite  | 11 of 268  | 4.1      |
| Questionable  | 10 of 269  | 3.7      |
| Intermittent claudication                             | 9 of 217   | 4.1      |

early periods to be significant. Many causes for male preponderance have been alleged, but none has impressive support. So far, this analysis throws no light on causes of sex difference in incidence, and indicates that probably there has been little change in sex ratio in thirty-one years.

TABLE III  
COEXISTING CONDITIONS

|  | INCIDENCE  | PER CENT |
|--|------------|----------|
| Sex  |            |          |
| Males  | 209 of 300 | 69.7     |
| Females  | 91 of 300  | 30.3     |
| Average age at onset, 61 years<br>(males 60.1; females 61.7) |            |          |
| Weight   |            |          |
| Obese  | 67 of 228  | 29.4     |
| Normal   | 112 of 228 | 49.1     |
| Thin   | 49 of 228  | 21.5     |
| Gallbladder disease  | 47 of 269  | 17.5     |
| Rheumatic valvular disease                                   | 11 of 300  | 4.7      |
| Syphilis   |            |          |
| Serological evidence   | 23 of 233  | 10.0     |
| History, serology, and anatomical                            | 33 of 300  | 11.0     |
| Miscellaneous  |            |          |
| Active tuberculosis  | 4 of 300   | 1.3      |
| Peptic ulcer   | 10 of 300  | 3.3      |
| Hemochromatosis  | 1 of 300   | 0.3      |
| Hodgkin's disease  | 1 of 300   | 0.3      |
| Leucemia   | 1 of 300   | 0.3      |

#### AGE

The age at onset of first infarction could be determined in 222 of the cases presented (see Fig. 2 for percentage distributions). The average age at onset for the whole group was 61, for males 60.1 and for females 61.7 years. The largest incidence in a single decade was in the seventh, in which 35 per cent occurred. Three decades, from 50 to 79, contained 83.7 per cent of the group. The number of cases in the sixth and eighth decades were nearly the same—56 and 52,

respectively. When the incidence of onset in decades is compared on the basis of sex (Fig. 3), it is seen that in the fifth decade there is a slight male preponderance and in the sixth a large one; while in the seventh decade there is a large female preponderance and in the eighth a slight one. Both males and females reach their peak in the seventh

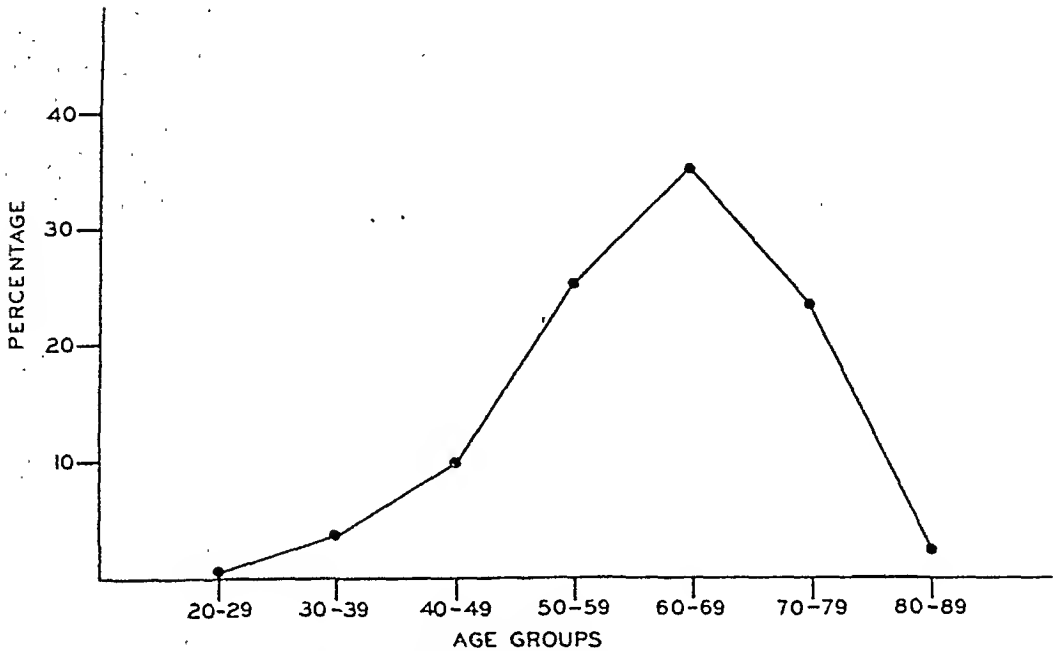


Fig. 2.—Age at initial infarction: Percentage of 222 patients having initial attack in different decades.

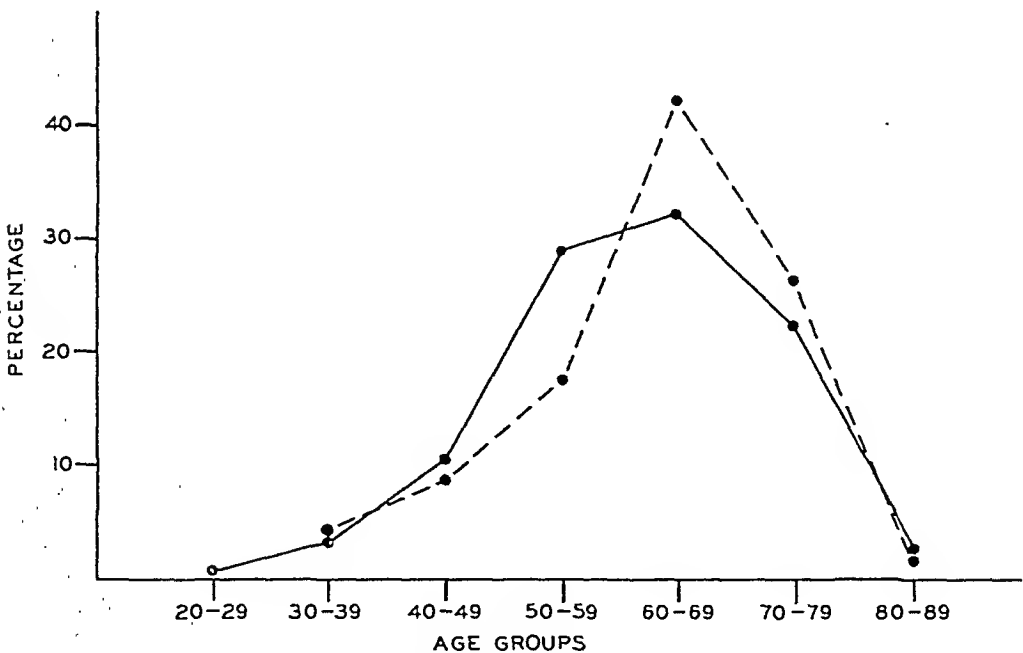


Fig. 3.—Age at initial infarction: Percentages of 153 males (solid line) and 69 females (broken line) in different decades.

decade. Such figures indicate a tendency for the males to have their initial occlusion at an earlier age in the group studied. It is possible that the delay in females is related to the menopause, since the peak in their incidence is two decades after the 40 to 49 decade. It could be correlated, however, with no factor in this analysis. Since the

incidence and severity of coronary disease increase in later decades, age has an important relation to infarction of the heart.

#### RACE AND COLOR

No record of race is available for hospital admissions over the thirty-one-year period, but several random one-year records show constancy among themselves and also when compared to the whole group. For distribution by race see Table IV. As for color, 283 were white, 16 colored, and 1 yellow. The Russians, definitely more than their proportion in the population, were Hebrews with two exceptions. There were 16 Hebrews. These figures cannot be interpreted as having undue importance, nor race be said to have any unusual rôle in genesis of coronary thrombosis in the cases studied.

TABLE IV  
DISTRIBUTION BY RACE

|   |           |
|---|-----------|
| American  | 168       |
| Irish   | 31        |
| Colored   | 16        |
| Canadian  | 16        |
| Russian   | 14        |
| English   | 13        |
| Scottish  | 6         |
| German  | 6         |
| Nova Scotian  | 5         |
| Italian   | 3         |
| Swedish   | 3         |
| Lithuanian  | 2         |
| Syrian  | 2         |
| Greek   | 2         |
| Portuguese  | 2         |
| One case each of French Canadian, Polish,<br>Norwegian, Finn, New Foundlander,<br>Armenian, Japanese, Turk, Latvian,<br>Swiss, Spaniard | 11        |
|   | <hr/> 300 |

#### HEREDITARY FACTORS

Much has been said concerning family tendency to diseases originating in arterial deterioration, and figures of varying impressiveness have been accumulated. The first case report of family tendency in coronary thrombosis was that of Riesman,<sup>41</sup> and a good summary of Musser and Barton<sup>35</sup> appeared in 1931. Goldsmith and Willius<sup>15</sup> obtained positive family history in 55 per cent of their recent series. White<sup>45, 47</sup> has called attention to the family tendency in cases of precocious coronary arteriosclerosis and to the association of moderate, but never marked hypertension, among Hebrews. In many of the present cases no satisfactory history was possible; in a few no relevant data were recorded. Among the 138 cases with satisfactory histories there were 55 instances of family cardiovascular renal disorder, 40 per cent. Nine

instances of apparent coronary thrombosis occurred ("acute indigestion," sudden death below forty-five years) in a parent. In 20, cerebral vascular accidents were known (stroke, "shock," apoplexy). In 14, a parent had died of dropsy or Bright's disease in the arteriosclerotic age period. The hereditary distribution of the 55 cases with positive family history is seen in Fig. 4. Hypertension was present in 70 per cent of this group, but in only 50 per cent of the entire series. Fifty-six per cent had their initial attack before the seventh decade, as compared with 39.2 per cent in the entire group (Fig. 5). From the literature and the data presented it appears that heredity is an important predisposing factor in coronary arteriosclerosis, and that hypertension is related.

#### BUILD AND WEIGHT

Levine has observed that the thin have less tendency to coronary or general sclerosis than the obese, and this observation is borne out by insurance tables, du Bray,<sup>12</sup> Dublin and Marks.<sup>11</sup> In this series build, or type, was not adequately described in a sufficient number of cases to be conclusive. Exact weight was recorded only in a small proportion. In 228, however, there was enough description of the weight so that an individual fell into the class of (1) obese and overweight, (2) well developed and nourished or (3) thin, emaciated, and undernourished. While this is not a wholly accurate gauge it has value because it is the clinical division into which cases naturally fall and are observed. Sixty-seven, or almost 30 per cent, were obese. Forty-nine, or 21.5 per cent, were thin. One hundred and twelve, or almost one-half, did not deviate from what was considered normal. Comparing the obese in relation to sex, 45 per cent were females and 55 per cent males, whereas only 31.1 per cent of the entire 228 were females—indicating a disproportionate number of females among the obese.

Many patients were thin, some were senile, others had hemiplegia or were physically or economically unable to gain more than fair subsistence. Twelve were victims of chronic disease (tuberculosis, endocarditis, gangrene). The age, sex, and incidence of hypertension of the thin group followed the general pattern. It is manifest that arterial disease is not prevented by thinness, or at least that those with arterial disease may become thin.

There is no available evidence bearing on Levine's belief that the typical patient is well-set, often somewhat overweight, frequently quite strong. In this series obesity occurred more frequently than in normal control groups; was relatively more frequent in women than in men. On the other hand, thinness conferred no immunity. The age at onset among thin, normal, or obese patients did not vary significantly from the group as a whole (Fig. 6). From the inconclusive data heredity does not seem to be necessarily related to body weight in predisposing to infarction.

## ASSOCIATED DISEASES

*Diabetes Mellitus.*—Diabetes mellitus is recognized as a disease of unusual importance in association with arteriosclerosis, and particularly with coronary thrombosis. Nathanson<sup>36</sup> observed coronary sclero-

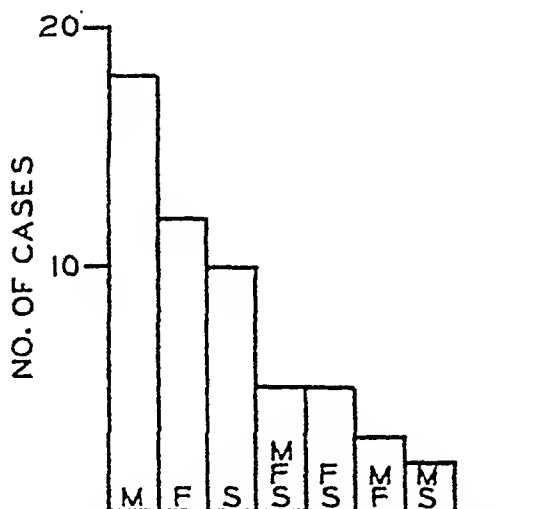


Fig. 4.—Hereditary distribution: Arranged according to the number of patients with involvement of mother, father, or siblings, and combinations. The mother had vascular disease in 28 instances, the father in 25, and siblings in 22 of a total of 55 patients with family vascular disease.

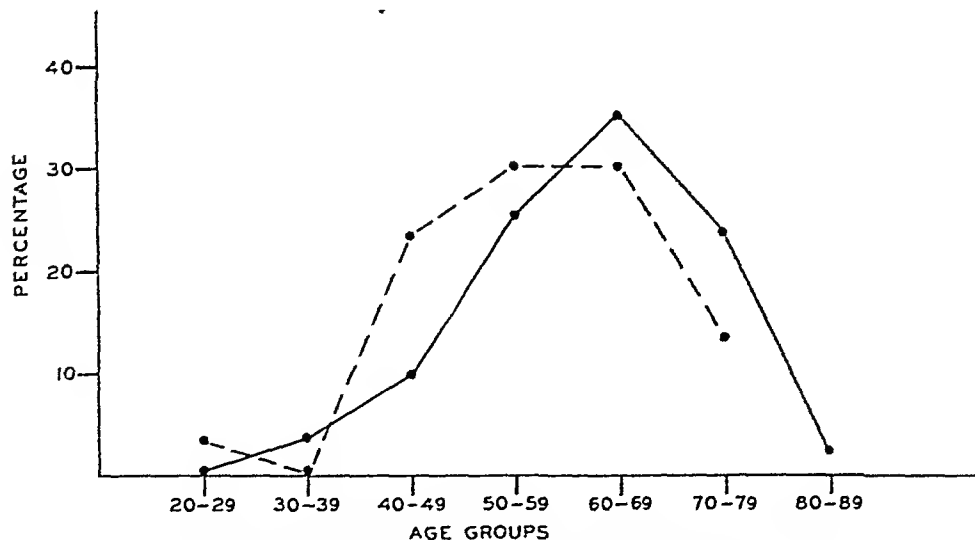


Fig. 5.—Age at initial infarction: Cases with family history (broken line) compared with the entire group of 222 (solid line).

sis in 41 of 100 autopsied diabetic cases. Joslin's figures<sup>21</sup> indicate that recently deaths from coronary disease are higher than those from cerebral or peripheral vascular lesions in diabetics. Insulin, by reducing the deaths from coma and the metabolic mistakes of diabetes, has prolonged life so that more diabetics live to the age when even non-diabetics are prone to develop arteriosclerosis.

Antecedent diabetes occurred in 10 per cent of Conner and Holt's 287 cases,<sup>9</sup> while in Levine's group there were 23.7 per cent with diabetes or transient glycosuria. In this series there were 19 diabetics out of 109 with satisfactory information on this point, 17.4 per cent.

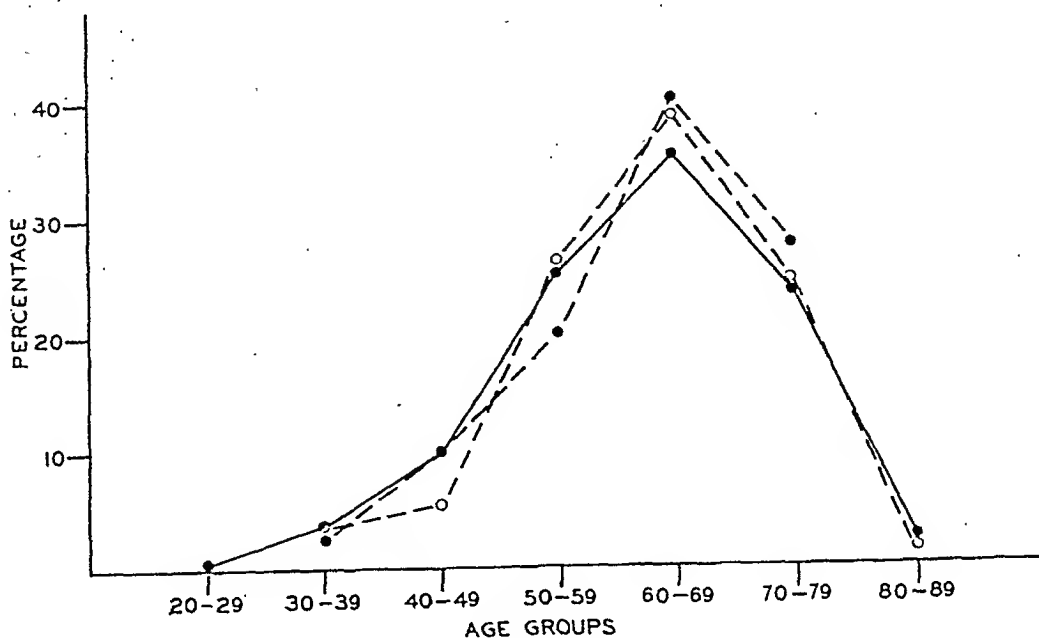


Fig. 6.—Age at initial infarction: Comparison of the obese (broken line—hollow circle), thin (broken line—solid circle), and the entire group (solid line).

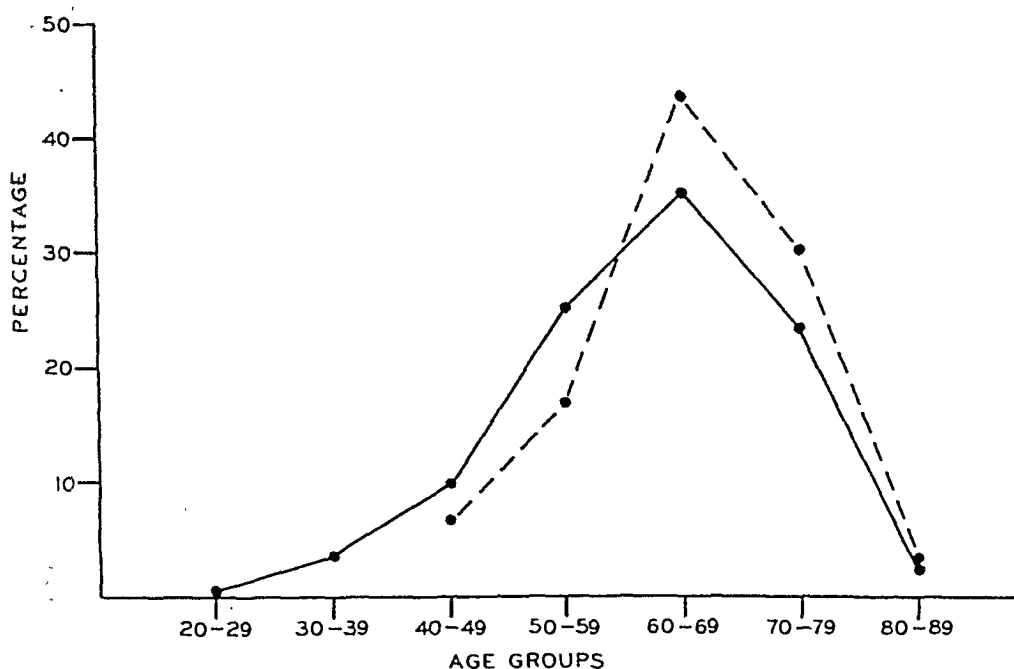


Fig. 7.—Age at initial infarction: Comparison of those with gallbladder disease (broken line) and the entire group (solid line).

Seven of the cases were female, the same proportion as in the whole group. The age at onset averaged one year older than in the general group, with the youngest 35, the oldest 84. Hypertension was present in seven, was not demonstrated in eleven, with no data in three. No instance of freedom of arteriosclerosis, generalized and coronary, was found, though the records are not complete in all cases. In 56 of the

300 patients there is no history on this point and no urine examination, so the incidence in the group may have been higher. Since the only constant finding in these diabetics was arterial disease, it is concluded that diabetes is important in the pathogenesis of coronary thrombosis only so far as it is associated with coronary sclerosis.

*Gallbladder Disease.*—Although cholecystitis is not primarily a metabolic disease, gallstone, especially of the cholesterol type, probably is secondary to a metabolic disorder,<sup>3, 4</sup> if not a primary fault.<sup>34</sup> Disease of the gallbladder was present in 47, or 17.5 per cent, of 269 patients in which this organ was mentioned. Twenty-one, or 44 per cent, of the cases were in females, a disproportionately large number. There were slight differences from the whole group in the incidence of onset in decades (Fig. 7). Obesity was present in seven, thinness in ten. An absolute correlation was found with arterial disease, since all with gallbladder disease had both general and coronary arteriosclerosis. The latter was extreme in twelve. Stone was present in 90 per cent of those with gallbladder disease, in some cases with little disturbance in the gallbladder structure. It seems probable that the high incidence of gallbladder disease and especially of stone formation is another manifestation, as is obesity, of a derangement of the lipid-cholesterol metabolism. Stone formation is not of etiological significance in arterial disease, but rather is an expression of a fundamental fault which underlies both processes.

*Rheumatic Fever.*—Karsner and Bayless,<sup>22</sup> after a review of the extensive literature, maintain that rheumatic fever regularly produces disease in the coronary arteries, inflammatory or fibrotic, or both, and suggest that it predisposes to early coronary sclerosis. The extent of coronary damage in rheumatic heart disease bears a roughly inverse relation to the size of the arteries, being most extensive in the small and less marked in the large ones.<sup>16</sup> The occurrence of rheumatic heart disease in this series is seen in Table V. Since only 3 of 31 instances of initial infarction before 50 were associated with disease, there is no evidence of precocious rheumatic coronary disease in this series, nor is there any indication that rheumatic fever of the type which produces valvular disease is a frequent precursor of coronary sclerosis leading to infarction.

TABLE V  
RHEUMATIC VALVULAR DISEASE

|   |    |
|---|----|
| History of rheumatic fever and rheumatic lesions    | 6  |
| No history of rheumatic fever but rheumatic lesions | 3  |
| Bacterial endocarditis                              | 5  |
| Total   | 14 |
| History of rheumatic fever and no rheumatic lesions | 13 |

*Syphilis*.—Syphilitic heart disease causes narrowing of the mouths of the coronary arteries. This is a recognized cause of cardiac infarction<sup>7</sup> but one that is not necessarily associated with thrombosis. White and Bland<sup>45</sup> found evidence of syphilis in 4 per cent of 200 cases of coronary thrombosis in private practice, Conner and Holt<sup>9</sup> in 14.2 per cent of their cases, Levy<sup>29</sup> in 13.4 per cent, and Parkinson and Bedford<sup>38</sup> in 9.6 per cent of 83 autopsies. Appelbaum and Nicolson,<sup>1</sup> who record an incidence of 6 per cent of 168 autopsies, observe "that modern pathologists do not regard syphilis as an etiological factor in the production of arteriosclerosis." For evidence of syphilis in this series see Table VI. Syphilitic structural changes were contributory to infarction in 8, or 2.7 per cent, of the entire 300 patients.

TABLE VI  
SYPHILIS

| EVIDENCE                                  | NO. OF CASES | PER CENT |
|---|--------------|----------|
| Serology positive                         | 23 (of 233)  | 10       |
| History positive                          |              |          |
| Negative serology (treated)               | 7            |          |
| No serology                               | 1            |          |
| Autopsy                                   |              |          |
| Aortitis (negative serology)              | 2            |          |
| Aortitis (positive serology)              | (8)          |          |
| Aortitis and aneurysm (positive serology) | (2)          |          |
| Total                                     | 33 (of 300)  | 11       |

#### ALCOHOL AND TOBACCO

The chronic users of alcohol and of tobacco in this series are tabulated in Table VII. Most of the addicts to either were males. The age at onset in the two groups followed the average quite closely. These figures do not indicate that alcohol and tobacco are regular etiological agents or that use, abuse, or abstinence specifically induces or prevents those lesions which determine coronary thrombosis and myocardial infarction. No light is thrown on White's<sup>46</sup> suggestion that tobacco may induce premature coronary disease in young non-hypertensive Hebrews who lead a sedentary life.

TABLE VII  
FACTS OF INTEREST IN HISTORY

| HISTORY                            | INCIDENCE | PER CENT |
|------------------------------------|-----------|----------|
| Family history of vascular disease | 55 of 138 | 40       |
| Use of alcohol                     |           |          |
| Excessive                          | 19 of 109 | 17       |
| Moderate                           | 47 of 109 | 43       |
| Abstainers                         | 43 of 109 | 40       |
| Use of tobacco                     |           |          |
| Excessive                          | 25 of 89  | 28       |
| Moderate                           | 35 of 89  | 39       |
| Abstainers                         | 29 of 89  | 33       |



## PRECIPITATING CONDITIONS

A degree of tardy prophylaxis against coronary thrombosis might be feasible if the immediate precipitating events were specific and could be avoided or delayed.

*Seasonal Variation.*—Very striking figures are reported by Wood and Hedley<sup>49</sup> for seasonal variation in onset of coronary thrombosis for three years at Philadelphia in a group of 133 patients. Seasonal variation in death rate has been noted by Bundesen and Falk<sup>6</sup> and by Cohn,<sup>8</sup> as well as in insurance statistics in cardiovascular disease. In this series a considerable monthly variation was found in incidence of acute attacks, with a high of 29 in April and a low of 11 in August. In cases with repeated infarcts, only those subsequent attacks separated by six months or more were included. When the seasonal incidence was observed, using the rough division of December, January, and February as winter, the next three months as spring, and so on, a more striking seasonal variation was found (Figs. 8 and 9). Attention is called to the low incidence of acute coronary occlusion in the summer. Fall, winter, and spring are each represented by high percentages. It is improbable that chance factors, such as hospital admissions or city population shifts in summer, played a large part in these results, as in many cases admission or death followed the onset by weeks, months, or years. The low summer incidence may be correlated with a number of factors, such as increases in temperature, decreases in infections, especially respiratory, or changes in diet. If further substantiation of this seasonal variation is found it may have an important bearing on therapy in arteriosclerotic disease of the coronary arteries.

TABLE VIII  
CIRCUMSTANCES AT ONSET

| Time of day                             |    |      |          |        |
|---|----|------|----------|--------|
| A.M.                                    | 28 |      |          |        |
| Noon                                    | 1  |      |          |        |
| P.M.                                    | 27 |      |          |        |
| Midnight                                | 3  |      |          |        |
| Total                                   | 59 |      |          |        |
| RELATION TO EXTERNAL ENVIRONMENT        |    | REST | ACTIVITY | EATING |
| Sleeping                                | 16 | 16   |          |        |
| Resting, reclining, awake               | 13 | 13   |          |        |
| Sitting quietly                         | 11 | 11   |          |        |
| Getting out of bed in A.M.              | 4  |      | 4        |        |
| Eating                                  | 4  | 4    |          | 4      |
| Shortly after eating<br>(some activity) | 10 |      | 10       | 10     |
| Moderate exercise                       | 19 |      | 19       |        |
| Severe exercise                         | 7  |      | 7        |        |
| Immediately after exercise              | 4  |      | 4        |        |
| Totals                                  | 88 | 44   | 44       | 14     |

*Time of Day.*—Marked changes in cardiovascular activity occur during the phases of daily life with exercise, digestion, emotion, and relaxation. From the data in Table VIII it is clear that time of day

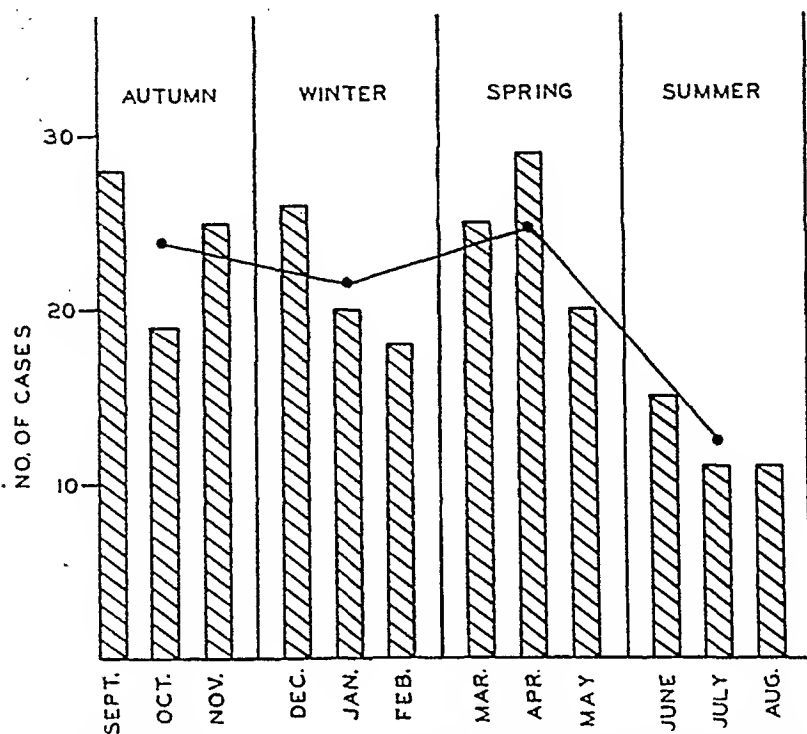


Fig. 8.—Seasonal variation: Number of acute attacks showing monthly distribution and the average for each season (black line) in 247 instances.

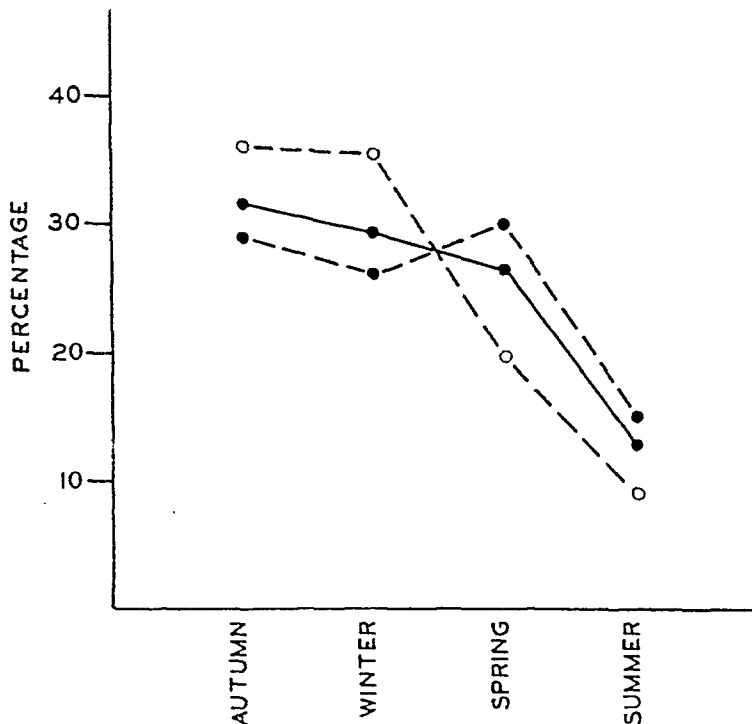


Fig. 9.—Incidence of acute attacks by seasons: Comparison of figures of Wood and Hedley, 133 attacks (broken line—hollow circle), and this series, 247 attacks (broken line—solid circle) and an average of the two series, 380 attacks (solid line—solid circle).

per se was not a factor in this series in determining onset of infarction.

*Occupation and Activity.*—Most of these patients gave evidence of physical wear and tear. The majority were laborers or housewives,

but analysis by occupational subgroups was not carried out. The state of activity or inactivity in which acute attacks occurred was examined. Belief that thrombosis *usually* occurs during rest<sup>21, 22, 23</sup> is not verified. It appears that no state of existence is safe when the underlying damage is present (Table VIII). There was no difference in precipitating events between those over 50 and those under. Men, by virtue of their daily work, were more frequently active, but women were also overtaken during considerable activity. Altogether in this group occupation or activity did not seem specifically important.

*Infection.*—Bronchitis was an extremely frequent finding, although no considerable number had bacteriological studies. The finding of bronchitis or bronchopneumonia at autopsy of course does not prove that it was present before the myocardial infarction, except in very recent cases. At least five patients had bronchopneumonia before infarction occurred. In two, empyema antedated infarction; in two chills had occurred before thrombosis; and in two lobar pneumonia was found. Although more careful studies of infection are necessary and no definite conclusion can be drawn, the suspicion is strong that infection may be a precipitating factor in some cases of thrombosis.

*Acute Effects of Alcohol and Tobacco.*—Four of the 19 chronic alcoholics definitely developed their initial thrombosis while deeply intoxicated. It is probable that two others had the same initiation. In 13 there was no relation. In the 47 moderate drinkers no association was noted. It is concluded that acute alcoholic coma may precipitate occlusion in certain instances where coronary disease already exists. There was no association in any case with the act of smoking, chewing, or using snuff.

*Trauma.*—Indirect trauma is a known cause of cardiac rupture<sup>24</sup> and has been rarely mentioned as a precipitating factor in occlusion.<sup>25</sup> In three cases in this series it was a possible direct factor. One patient fell from a ladder 8 feet high, striking his chest and fracturing several ribs on the left side. No pain was described before the fall. He suffered severe pain for days. Ten weeks after the fall he died and a fairly recent infarct with early aneurysmal dilatation was discovered. Another fell and hurt his left side in a bath tub, and having suffered undue pain went directly into cardiac failure though there had been neither pain nor failure before. At death, after almost two years, a large myocardial scar was found. In a third case a fall from a ladder resulted in fractured skull. At autopsy, eight days later, old and recent infarcts were found. In the first two cases it is possible that physical violence with changes in intrathoracic pressure and volume, and the reflexes and circulatory disturbances set up by the accident or the shock, may have precipitated thrombosis on the basis of pathological changes which already existed. The rôle of trauma in the third case is not so clear-cut.

*Hypoglycemia.*—It is recognized that insulin shock may induce coronary thrombosis, as may even sudden reductions of blood sugar without evidence of shock.<sup>2, 13</sup> Probably more than one factor is involved in the mechanism, including peripheral vascular collapse and physiochemical changes in the blood. Insulin was used in all 19 of the diabetics of this series, vigorously in seven. In three it was the most probable precipitating factor in initiating the thrombosis. No case of spontaneous hypoglycemia, such as has been described by Harris (quoted by Harrison<sup>18</sup>), was found in this series. Diabetic coma was associated with one case of thrombosis, but it is not clear which condition appeared first.

*Nitroglycerin.*—Since 1863, when Lauder Brunton<sup>5</sup> introduced them for relief of angina pectoris, nitrites have been used freely for relief of cardiac pain. With the clinical recognition of coronary thrombosis it was noted that this disease was rarely relieved, and even might be aggravated by the nitrites.<sup>40</sup> In many cases of this series nitroglycerin was used in small amounts (1 to 4  $\frac{1}{100}$ -grain tablets), usually with no relief. Two patients took heroic amounts, one 20 tablets, the other 50, over short periods of time before coming to the hospital. If it did not inaugurate it probably did aggravate the condition, since the dilatation, which is necessarily minimal in calcified coronaries, must have been counterbalanced by the disproportionate fall in blood pressure.

*Operative Trauma and Shock.*—Surgeons, in focusing attention on mistaken diagnoses of acute abdominal conditions where coronary thrombosis exists, have not stressed the danger of operative and anesthetic trauma in inducing thrombosis. Master<sup>33</sup> has recently emphasized the rôle of surgical procedures in inducing infarction, but Levine<sup>28</sup> did not mention it in a study of nine postoperative cardiac disturbances (all arrhythmias)—cases of what had long been called “acute dilatation of the heart.” In this series there were eight cases following major operations; in four, the postoperative period was associated with shock, and death resulted from a fresh infarction, while in the remainder the relation was not so clearly established. In one, following a minor procedure (thoracotomy), infarction occurred.

*Hemorrhage.*—In one case hemorrhage from a peptic ulcer (with vomiting and retching) was followed by shock, for which several transfusions were given. At autopsy a fresh infarct was found. The suspicion of transfusion reaction cannot be eliminated, but hemorrhagic shock seemed to be the precipitating agent. In another, severe epistaxis was followed by markedly reduced hemoglobin and a fresh infarct was found after death. Two others had profound anemia, with hemoglobin below 35, but no certain relation with the coronary thrombosis could be proved.

*Miscellaneous.*—One patient went into collapse following decompression of the bladder, long distended by chronic prostatic obstruction,

and died with a fresh infarct. In one case with lymphatic leucemia, injection of pentnucleotide was followed by substernal constriction. Nine days later the patient died and a recent infarct was found.

Though in the minds of clinicians the grave form of vascular collapse in cardiac infarction is regularly assumed to be a result, not a cause, of the condition, these cases demonstrate that collapse may be the catalyst in precipitating thrombosis and, continuing, color the clinical picture after infarction has occurred.

TABLE IX  
INTERNAL DISTURBANCES

|   |     |
|---|-----|
| Operative trauma and shock              | 5   |
| Alcoholic coma                          | 4   |
| Insulin hypoglycemia                    | 3   |
| After trauma to chest                   | 2   |
| After trauma to head?                   | 1   |
| After excessive nitroglycerin           | 2   |
| Posthemorrhagic shock                   | 2   |
| After bladder decompression             | 1   |
| Diabetic coma?                          | 1   |
| Transfusion reaction?                   | (1) |
| Pentnucleotide reaction?                | 1   |
|   | —   |
| Vascular collapse or related conditions | 22  |

#### SUMMARY AND CONCLUSIONS

The criteria for selection of 300 cases of infarction of the heart are given and the associated vascular lesions are discussed.

The average age at onset in 222 patients was 61 years, 60.1 for males and 61.7 for females.

Of the entire group of patients, 91, or 30.3 per cent, were females and 209 were males. Proportionately more males had their original attack in the fifth and sixth decades, and more females in the seventh and eighth.

Family tendency to cardiovascular disease was an important factor, appearing in 40 per cent of 138 patients. Seventy per cent of this subgroup had hypertension, whereas only one-half of the entire series had it. The age at onset in those with family tendency was younger than in the rest.

Weight, as judged by division into obese, normal, and thin groups, had no specific effect in predisposing to or protecting from thrombosis. Obesity was abnormally prominent, but thinness also was frequent and conferred no relative immunity.

Diabetes was present in 17.4 per cent of 109 patients, but was not characterized by earlier age of onset. No diabetic was exempt from arteriosclerosis. Gallbladder disease, especially with stone formation, occurred in relatively more females than males, was present in 17.5 per cent of 269 patients, and was always associated with arterio-

sclerosis. Rheumatic heart disease was an unimportant factor in this series. Syphilis, evidence for which was present in 10 per cent of 233 patients, was the direct or facilitating cause of infarction in eight.

The chronic use of alcohol or tobacco could not be regarded as etiologically important. In a few cases alcoholic coma seemed a precipitating factor. The seasonal incidence of onset of infarction was low in the summer months. Time of day, occupation, and activity appeared unrelated to the onset of thrombosis.

Attention is called to the danger of surgical or medical shock as an immediate precursor and precipitating agent in coronary thrombosis when disease already exists in the coronary arteries.

The author wishes to express his sincere appreciation to Dr. Soma Weiss for inspiration and valuable assistance during the preparation of this paper.

#### REFERENCES

1. Appelbaum, E., and Nicolson, G. H. B.: Occlusive Diseases of the Coronary Arteries, *AM. HEART J.* 10: 662, 1935.
2. Blottner, H.: Coronary Disease in Diabetes Mellitus, *New England J. Med.* 203: 709, 1930.
3. Boyd, W.: Pathology of Internal Disease, Philadelphia, 1931, Lea & Febiger.
4. Boyd, W.: Studies in Gall Bladder Pathology, *Brit. J. Surg.* 10: 337, 1923.
5. Brunton, T. L.: The Use of Nitrite of Amyl in Angina Pectoris, *Lancet* 1: 48, 1867; *ibid.*, p. 97.
6. Bundesen, H. N., and Falk, I. S.: Low Temperature, High Barometer and Sudden Death, *J. A. M. A.* 87: 1987, 1926.
7. Cannon, J. H.: Syphilitic Coronary Occlusion in Aortic Insufficiency, *AM. HEART J.* 5: 93, 1929.
8. Cohn, A. E.: Heart Disease From the Point of View of the Public Health, *AM. HEART J.* 2: 275, 1927.
9. Conner, L. A., and Holt, E.: The Subsequent Course and Prognosis in Coronary Thrombosis. An Analysis of 287 Cases, *AM. HEART J.* 5: 705, 1930.
10. Cowdry, E. V.: Arteriosclerosis, a Review of the Problem, New York, 1933, The Macmillan Company.
11. Dublin, L. I., and Marks, H. H.: The Influence of Weight on Certain Causes of Death, *Human Biol.* 2: 159, 1930.
12. Du Bray, E. S.: Comments on Body Weight in Relation to Health and Disease, *Am. J. M. Sc.* 170: 564, 1925.
13. Enklewitz, M.: Diabetes and Coronary Thrombosis, *AM. HEART J.* 9: 386, 1934.
14. Freyberg, R. H., Newburgh, L. H., and Murrill, W. A.: Cholesterol Content of Blood in Diabetic Patients Fed Diets Rich in Fat, *Arch. Int. Med.* 58: 589, 1936.
15. Goldsmith, G. A., and Willius, F. I.: Bodily Build and Heredity in Coronary Thrombosis, *Ann. Int. Med.* 10: 1181, 1937.
16. Gross, L., Kugel, M. A., and Epstein, E. Z.: Lesions of the Coronary Arteries and Their Branches in Rheumatic Fever, *Am. J. Path.* 11: 253, 1935.
17. Hamman, L.: The Symptoms of Coronary Occlusion, *Bull. Johns Hopkins Hosp.* 38: 273, 1926.
18. Harrison, T. F.: Failure of the Circulation, Baltimore, 1935, The Williams & Wilkins Company.
19. Hughes, F. W. T., and Perry, C. B.: Senile Arterial Changes in a Child Aged Seven Weeks, *Bristol Med.-Chir. J.* 46: 219, 1929.
20. Jamison, S. C., and Hauser, G. H.: Angina Pectoris in a Youth of Eighteen, *J. A. M. A.* 85: 1398, 1925.
21. Joslin, E. P., Root, H. F., White, P. D., and Marsh, A.: The Treatment of Diabetes Mellitus, ed. 5, Philadelphia, 1935, Lea & Febiger, p. 175.
22. Karsner, H. T., and Bayless, F.: Coronary Arteries in Rheumatic Fever, *AM. HEART J.* 9: 557, 1934.
23. Leary, T.: Experimental Atherosclerosis in the Rabbit Compared With Human (Coronary) Atherosclerosis, *Arch. Path.* 17: 453, 1934.

24. Leary, T.: Atherosclerosis, the Important Form of Arteriosclerosis; a Metabolic Disease, *J. A. M. A.* 105: 475, 1935.
25. Lemann, J. L.: Coronary Occlusion in Buerger's Disease (Thrombo-Angiitis Obliterans), *Am. J. M. Sc.* 176: 897, 1928.
26. Levine, S. A., and Brown, C. L.: Coronary Thrombosis: Its Various Clinical Features, *Medicine* 8: 245, 1929.
27. Levine, S. A., and Tranter, C. A.: Infarction of the Heart Simulating Acute Surgical Abdominal Conditions, *Am. J. M. Sc.* 155: 57, 1918.
28. Levine, S. A.: Acute Cardiac Upsets Occurring During or Following Surgical Operations, *J. A. M. A.* 75: 795, 1929.
29. Levy, R. L., Brunn, H. G., and Kurtz, D.: Facts on Disease of the Coronary Arteries, Based on a Survey of the Clinical and Pathologic Records of 762 Cases, *Am. J. M. Sc.* 187: 376, 1934.
30. Levy, R. L.: Diseases of the Coronary Arteries and Cardiac Pain, New York, 1936, The Macmillan Company.
31. Lewis, T.: Diseases of the Heart, New York, 1933, The Macmillan Company.
32. Luten, D.: Contributory Factors in Coronary Occlusion, *AM. HEART J.* 7: 36, 1931.
33. Master, A. M., Dack, S., and Jaffe, H. L.: Coronary Thrombosis: An Investigation of Heart Failure and Other Factors in Its Course and Prognosis, *AM. HEART J.* 13: 330, 1937.
34. Meutzer, S. H.: The Pathogenesis of Biliary Calculi, *Arch. Surg.* 14: 14, 1927.
35. Musser, J. H., and Barton, J. C.: The Familial Tendency of Coronary Disease, *AM. HEART J.* 7: 45, 1931.
36. Nathanson, M. H.: Coronary Disease in 169 Autopsied Diabetics, *Am. J. M. Sc.* 183: 495, 1932.
37. Newburgh, L. H., and Clarkson, S.: Production of Arteriosclerosis by Diets Rich in Animal Proteins, *J. A. M. A.* 79: 1106, 1922.
38. Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, *Lancet* 1: 4, 1928.
39. Phipps, C.: Contributory Causes of Coronary Thrombosis, *J. A. M. A.* 105: 761, 1936.
40. Procter, S. H., and Ayman, D.: Harmful Effects of Nitroglycerine, *Am. J. M. Sc.* 184: 480, 1932.
41. Riesman, D.: Coronary Thrombosis: With an Account of the Disease in Two Brothers, and Remarks Upon Diagnosis and Treatment, *M. Clin. North America* 6: 861, 1923.
42. Samuels, S. S., and Feinberg, S. C.: The Heart in Thrombo-Angiitis Obliterans, *AM. HEART J.* 6: 255, 1931.
43. Swineford, O., Jr.: Multiple Rupture of Heart by Indirect Trauma, Complicated by Mural Thrombosis and Embolism, *AM. HEART J.* 8: 418, 1933.
44. Wearn, J. T.: Thrombosis of the Coronary Arteries With Infarction of the Heart, *Am. J. M. Sc.* 165: 259, 1923.
45. White, P. D., and Bland, E. F.: A Further Report on the Prognosis of Angina Pectoris and of Coronary Thrombosis. A Study of Five Hundred Cases of the Former and of Two Hundred Cases of the Latter, *AM. HEART J.* 7: 1, 1931.
46. White, P. D., and Sharber, T.: Tobacco, Alcohol, and Angina Pectoris, *J. A. M. A.* 102: 655, 1934.
47. White, P. D.: Coronary Disease and Coronary Thrombosis in Youth, *J. M. Soc. of New Jersey* 32: 596, 1935.
48. Wilhelmy, E. W., and Helwig, F. C.: Clinical and Pathologic Studies of Coronary Disease, *J. Missouri M. A.* 32: 476, 1935.
49. Wood, F. C., and Hedley, O. F.: The Seasonal Incidence of Acute Coronary Occlusion in Philadelphia, *M. Clin. North America* 19: 151, 1935.

## THE INCIDENCE OF MYOCARDIAL INFARCTION WITHOUT PAIN IN 200 AUTOPSIED CASES\*

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IT IS the purpose of this study to determine the incidence of myocardial infarction not associated with pain. At the outset it is necessary to distinguish the symptom designated as pain from other distressing sensations in the chest. The main interest will be centered about those instances in which there was neither pain nor any uncomfortable sensation in the chest. There have been many references in the recent literature to cases of painless coronary thrombosis, but for the most part accurate analyses of other distressing sensations referable to the chest have not been made. In fact it seemed that when an adequate survey of such patients could be made, the occurrence of coronary thrombosis without any of the painful or uncomfortable sensations was by no means as common as had been intimated in recent reports.

In a study based upon 83 cases of coronary thrombosis and cardiac infarction, proved at autopsy, Parkinson and Bedford<sup>13</sup> pointed out that in a certain group of cases pain is not a prominent symptom. The number or frequency of these cases is not given. East, Bain, and Cary<sup>5</sup> reported 8 cases of cardiac infarction with no history of pain. Six of these cases were confirmed at autopsy. Davis<sup>4</sup> in a series of 76 cases found no history of pain in 29, or 38 per cent. Eleven patients who died suddenly were not included in the 29 without pain. Fifty-three of the 76 were confirmed by post-mortem examination. Bruenn, Turner, and Levy<sup>1</sup> found in a series of 33 autopsied cases that after discarding two patients from whom no history was available because they died in coma, 12 (39 per cent) of the remaining 31 had pain with the attack of coronary thrombosis. They found four patients with cardiac aneurysm who had had no pain associated with the final complete occlusion. Katz and his coworkers<sup>14</sup> in a study of 34 cases of coronary thrombosis examined at autopsy found that 13 (38 per cent) of these "did not give any history of cardiac pain." He pointed out, however, that congestive heart failure, debilitating disease or clouded sensorium may explain the absence of pain in a few of these patients but not in the majority.

Other authors have pointed out that myocardial infarctions may occur without pain, but have not indicated their frequency. Wearn,<sup>16</sup> Herrick,<sup>10</sup> Levine and Brown<sup>11</sup> and others<sup>2, 3, 7-9, 12, 15, 17 and 18</sup> have in-

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licated clearly the occurrence of such cases. Recently there have been many case reports of painless coronary occlusion, most of which have not been proved by post-mortem examination.

The material from which this study was made consisted only of cases of myocardial infarction that were proved by post-mortem examination. The records of the department of pathology of the Peter Bent Brigham Hospital from 1913 to January 1936 were reviewed, and the clinical case histories of every patient receiving a pathological diagnosis of either coronary thrombosis or myocardial infarction were studied critically, and any reference to pain or painful sensation was carefully noted. In most cases the infarct was either the direct cause of death or contributed to it, but in some it was an incidental finding at autopsy and was entirely unrelated to the cause of death. The total number of hearts with such post-mortem diagnoses was 200. Those hearts having infarctions of smaller size than 1 cm. in diameter were not included.

It was found that in some of these cases the clinical history was not satisfactory with regard to establishing clearly whether or not the patient experienced pain. As this point is a crucial one in this study, it was necessary to omit certain cases in order to include only those certainly not associated with pain. For example, it is obviously impossible to establish clearly whether a patient dying suddenly as a result of a myocardial infarction or one having an infarction while in uremic acidosis has experienced pain with the infarction. These and similar cases when omitted are specifically mentioned.

For the purpose of study the cases were divided into two groups according to the age of the infarct. In many instances it was possible to differentiate accurately two or more sites of infarction in the same heart. Counting each of these sites as a separate infarct there was in 200 autopsies a total of 251 separate infarcts which were quite definite. All these infarcts were divided into two groups, according to their approximate age; one consisting of lesions which were of recent origin and showing evidence of acute myocardial damage, the other consisting of lesions of longer duration, with evidence of a healed, fibrous connective tissue scar. The former were all less than eight weeks old and the latter were of much longer duration. Most of the infarcts fell easily into one of these two groups. However, there were several which were in such a state of healing that they had evidence of both fairly recent myocardial damage and of healing in the same area. The gross and, more important, the microscopic appearances of the infarcts in these cases were compared with the appearances of those in which the onsets were known to have occurred not more than six or eight weeks before the time of death. In this way doubtful cases were judged to fall in the old or recent groups. Those cases which had a clear, uncomplicated, clinical history of myocardial infarction were placed in the group of "old" or "recent" cases according to whether the infarction occurred

prior to six to eight weeks before death or not. Those cases having an indefinite onset and those in which the time of onset was not known accurately were placed in the proper group according to the age of the infarct judged by its appearance. According to this arbitrary division there were, in 200 patients, 109 old and 142 recent infarcts. In 51 hearts of this series both old and recent infarcts were found.

The cases of each group were divided according to whether or not the onset of the infarction was associated with pain. It was found that a great many had subjective sensations which were uncomfortable and disagreeable but were not described as painful. A further subdivision, therefore, was necessary to separate those actually having experienced pain from those having less severe sensations which were termed discomfort or distress.

#### GROUP OF "RECENT" INFARCTS

The total number of recent infarcts was 142. There were 48 cases in this group which had histories unsatisfactory in regard to establishing clearly whether the patient experienced pain at the time of the infarction. In these there were associated or complicating conditions which obscured the onset of the infarction or made it impossible to obtain a satisfactory story from the patient. The cases which were omitted because of unsatisfactory histories were as follows: sudden death 19; uremia 5; deep diabetic acidosis or coma 3; irrational, toxic, stuporous, delirious 9 (these included overwhelming infections of the peritoneum or blood stream, psychoses, and one case of peritonitis from ruptured gallbladder); cerebral embolism or cerebral hemorrhage 5; during or soon after surgical anesthesia and operation 4; during shock from bleeding duodenal ulcer 1; severe cachexia from widespread tuberculosis and amyloid disease 1; case in which heart was brought into pathology department for examination with inadequate history 1.

The 94 remaining cases all had satisfactory histories. The frequency of pain or discomfort is indicated in Table I.

It is apparent that only about 4 per cent of the cases had no pain or distress in the chest and not more than 4 per cent complained merely of discomfort. In fact over 90 per cent had a clear-cut history of chest pain. When pain did occur, the most common site was in the midsternum, although it occurred in all parts of the chest and not infrequently in the upper abdomen. In the four cases having "discomfort only" the sensations were described as "constriction in the thorax," "dull ache in the chest," "preordial discomfort and feeling of constriction," "marked substernal pressure." None was associated with pain. The case histories of the four instances in which it was definitely known that the attack of coronary thrombosis was unassociated with any discomfort in the chest are of sufficient interest to merit brief description.

TABLE I

|                                  | RECENT<br>INFARCTS |               | OLD<br>INFARCTS |               |
|----------------------------------|--------------------|---------------|-----------------|---------------|
|                                  |                    |               |                 |               |
| Cases with pain                  | 86                 | 91.0 per cent | 65              | 63.7 per cent |
| Cases with discomfort only       | 4                  | 4.3 per cent  | 14              | 13.7 per cent |
| Cases without pain or discomfort | 4                  | 4.3 per cent  | 23              | 22.5 per cent |

The first patient, a man aged sixty-four (Med. No. 22444), entered the ward greatly dyspneic and gasping for air and was asked if he had any pain. He cried, in answer, "No, I haven't any pain, but give me air!" He died a few minutes later and at autopsy had a large, very recent infarct near the apex of the heart in the left ventricle and no evidence of pulmonary embolism.

The second patient, a woman aged fifty (Med. No. 25374), had an incidental story of angina pectoris and was under observation for myxedema which was her primary complaint. She had been on the ward for several weeks and had been quite well during that time, when her condition suddenly changed. Without warning she became weak, semi-stuporous and was aroused with difficulty; her pulse became weak; heart sounds faint, and she "lay as if exhausted" for several days. After this she was very much improved and became well enough to sit up in a wheel chair. She denied having had any pain. Two weeks after the episode of weakness she died suddenly, and at autopsy there was found an infarct which contained necrotic muscle fibers and many phagocytic cells laden with pigment; in some areas the degenerated muscle fibers were being replaced with loose connective tissue. The appearance was of such an age that it could not have been the cause of sudden death, but from its appearance must have been several weeks old. There was no pulmonary embolus.

The third patient, a man aged seventy-four (Med. No. 2741), while in the excitement of hurrying to get a doctor for his wife, became suddenly short of breath, very weak, and it was necessary for him to sit down and rest several times before returning home. For several hours he continued to be weak and dyspneic and was nauseated but experienced no pain. Six days later he died suddenly. At autopsy there was a moderate sized, soft, necrotic infarct of the myocardium which had ruptured filling the pericardium with blood, causing his sudden death.

The fourth patient, a man aged seventy-seven (Med. No. 46956), with a history of a "feeling of depression in the chest with exertion and emotion" for two years, entered the ward complaining of weakness. He had signs of moderate cardiac decompensation, was given digitalis and twelve hours after admission was looking better, when he suddenly began to complain of increasing dyspnea. Respiratory difficulty, which was his only symptom, rapidly increased, and he died thirty minutes later without ever experiencing pain. At autopsy the right coronary

artery was completely occluded, and there was extensive recent infarction of the right ventricle. In addition there was an old infarct in the left ventricle near the apex. There was no pulmonary embolus.

It is of considerable interest that the most prominent symptom in two of these cases was the sensation of being short of breath, in another weakness was most prominent, and the other patient experienced both dyspnea and weakness.

#### GROUP OF "OLD" INFARCTS

The total number of old infarcts was 109. In seven of these cases the history was given by someone other than the patient. This occurred when the patient was brought to the ward in a comatose or irrational state and never regained consciousness, or when an emergency operation was to be performed from which the patient did not recover. In addition, there was one case in which the patient died outside the hospital, and the pathological specimen was brought in for examination without adequate history. Omitting these seven cases, which were not considered satisfactory in establishing whether the patient experienced pain with the infarct, there were 102 which had satisfactory histories (Table I).

There were 63.7 per cent of the patients who had a definite history of chest pain, 13.7 per cent with only a history of discomfort, and 22.5 per cent in whom there was no distress whatever. It is also of importance that 10 patients gave a history *only* of angina pectoris (that is, with transient pain of several minutes' duration) and had no story of the usual clinical appearance of coronary thrombosis. That this may occur was pointed out by Eppinger and Levine<sup>6</sup> in a recent communication.

The types of discomfort experienced by the group having a history of "discomfort only" were of considerable interest. They were described in the patients' own words, when possible, as follows: "sense of constriction in the chest," "some general discomfort in the abdomen," "biliousness which caused me to faint," "heart burn," "aching in the left chest, never severe," "dull pains in the abdomen," "gnawing at the lower end of sternum," "arm aches and numbness of the fingers of the left hand, of the left hand and arm," "tight band around lower part of chest pushing everything up," "substernal choking sensation and pressure in chest," "weight in chest," "tightness in chest," "indigestion and discomfort in stomach," "pressure in chest." It is surprising that infarction of the myocardium could give such a variety of sensations.

It is felt that the data obtained from the study of the old infarcts may not be as reliable as those of the recent infarcts. The first reason for this is that most of the patients were in the older age groups where memory defects may influence the recollection of a sensation experienced

in the past, especially if it was not severe. Secondly, it may well be that if a more deliberate inquiry had been made, a larger number would have been found to have experienced typical coronary pain or discomfort. However, this criticism partly loses its effectiveness when applied to the group of recent infarctions.

From this review it seems that there will be a small, but significant group of patients who had an old myocardial infarction from which they recovered, and in which there will be no history of chest pain or distress available to identify the attack. This percentage, it is felt, would be a good deal less than the 22.5 per cent found here with more careful analysis of the past history. Whether the incidence would be further influenced if minor infarctions less than 1 cm. in diameter were included, remains unanswered.

For the most part one can regard the old infarcts as synonymous with those from which recovery has occurred and the recent infarcts as the fatal ones. In this sense painless infarctions may be somewhat more frequent in the nonfatal than in the fatal group, but even here with more complete study the difference very likely will be only slight. These observations are mentioned because some authors have felt that painless infarction occurs almost entirely in those who have suffered from a previous attack.

#### SUMMARY AND CONCLUSIONS

A review was made of 200 consecutive autopsied cases of myocardial infarction. The purpose was to determine the incidence of painless cases of coronary thrombosis and the relative frequency of pain and other distressing symptoms in the chest. Most of the previously published reports, which have indicated that painless coronary thrombosis was of fairly frequent occurrence, have failed to take into account the difficulty of obtaining an adequate history under such conditions as sudden death, coma, surgical anesthesia, and cerebral vascular accidents. They have also omitted the important distinction between pain and other sensations equally characteristic of coronary artery disease, such as pressure, constriction, and burning.

The cases of myocardial infarction were divided into "recent" (and for the most part the immediate cause of death) and "old" (from which recovery for varying lengths of time occurred).

In the 200 cases of this series, when an opportunity was available to obtain an adequate history, it was found that only about 4 per cent of the attacks of myocardial infarction occurring within eight weeks before death were really painless. An analysis of the "old attacks" from which recovery had occurred showed that about 22 per cent were painless. It is believed that this figure would be a good deal lower if a more accurate account of the previous illness could have been obtained.

It was also found that about 4 per cent of the recent and about 14 per cent of the old infarctions were accompanied by sensations described by a variety of terms, such as, constriction in the chest, discomfort in the chest, burning, pressure, choking, or indigestion. About 10 per cent of the old infarctions had pain but not any more than is associated with an ordinary attack of angina pectoris. Ninety-one per cent of the recent and 64 per cent of the old cases had the classical pain of a coronary attack.

It was striking that about one third of the cases of acute infarction were accompanied by circumstances which made it impossible to elicit a history of pain. It is obvious that such cases cannot be classified in the painless group.

I wish to express my thanks to Professor Henry A. Christian and Dr. Samuel A. Levine for their aid in the preparation of this paper.

#### REFERENCES

1. Bruenn, H. G., Turner, K. B., and Levy, R. L.: Notes on Cardiac Pain and Coronary Disease, *AM. HEART J.* 11: 34, 1936.
2. Christian, H. A.: Cardiac Infarction (Coronary Thrombosis); An Easily Diagnosable Condition, *AM. HEART J.* 1: 129, 1925.
3. Coombs, C. F., and Hadfield, G.: Ischaemic Necrosis of the Cardiac Wall, *Lancet* 210: 14, 1926.
4. Davis, N. S.: Coronary Thrombosis Without Pain: Its Incidence and Pathology, *J. A. M. A.* 98: 1806, 1932.
5. East, C. F. T., Bain, C. W. C., and Cary, F. L.: Cardiac Infarction Without Pain—A Series of 8 Cases, *Lancet* 215: 60, 1928.
6. Eppinger, E. C., and Levine, S. A.: Angina Pectoris, *Arch. Int. Med.* 53: 120, 1934.
7. Gallavardin, M. L.: Symptomes et Diagnostic de l'infarctus du Myocarde, *J. de Méd. de Lyon* 2: 913, 1921.
8. Gibson, A. G.: The Clinical Aspects of Ischaemic Necrosis of the Heart Muscle, *Lancet* 209: 1270, 1925.
9. Hay, John: Certain Aspects of Coronary Thrombosis, *Lancet* 225: 787, 1933.
10. Herrick, J. B.: The Coronary Artery in Health and Disease, *AM. HEART J.* 6: 589, 1931.
11. Levine, S. A., and Brown, C. L.: Coronary Thrombosis: Its Various Clinical Features, *Medicine* 8: 245, 1929.
12. Levy, R. L.: Diseases of the Coronary Artery and Cardiac Pain, New York, 1936, The Macmillan Company.
13. Parkinson, J., and Bedford, D. E.: Cardiac Infarction and Coronary Thrombosis, *Lancet* 214: 4, 1928.
14. Saphir, O., Priest, W. S., Hamburger, W. W., and Katz, L. N.: Coronary Arteriosclerosis, Coronary Thrombosis and the Resulting Myocardial Changes, *AM. HEART J.* 10: 595 and 762, 1935.
15. Stenn, F.: Painless Coronary Occlusion, *Illinois M. J.* 67: 381, 1935.
16. Wearn, J. T.: Thrombosis of the Coronary Arteries, With Infarction of the Heart, *Am. J. M. Sc.* 165: 250, 1923.
17. White, P. D.: Heart Disease, New York, 1937.
18. White, S. M.: Non-Painful Features of Coronary Occlusion, *Ann. Int. Med.* 8: 690, 1934-35.

# THIOCYANATE THERAPY IN HYPERTENSION INCLUDING A NEW MICROMETHOD FOR DETERMINING BLOOD THIOCYANATES\*

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ARTICLES by Barker<sup>1, 2</sup> appeared in March, 1936, and January, 1937, describing the use of thiocyanate in the treatment of hypertension. Although thiocyanate has been employed for this purpose for nearly ten years, occasional fatalities have been reported, with the result that its use had been abandoned almost entirely. Barker attempted to control the dosage by determining the level of thiocyanate in the blood. He tried to maintain a level, of 6 to 12 mg. per 100 c.c. of serum, but stated that mild toxic symptoms did not occur until the level rose above 15 mg., more marked symptoms above 20 mg., while fatalities probably occurred only with a level of 40 to 50 mg. He found that there was great variation in dosage required to attain the same blood level in different individuals and suggested that this might account for the fatalities reported in the literature. In his series of 45 cases controlled by blood determinations, he had no fatalities. Serious complications occurred in two patients in whom the blood level rose unexpectedly to 33 and 45 mg., respectively, on what appeared to be conservative dosage.

Approximately two weeks after the publication of Barker's first paper we began using his method in patients attending the Cardiac Clinic of the University Hospital. We have also treated a few patients from the wards of this hospital and from private practice. In the beginning we used Barker's method for thiocyanate determination. We found, however, that many patients objected to the repeated venipunctures required. Recently we have modified Barker's method so as to be able to use small amounts of blood such as can be obtained by finger puncture.

## METHOD

*General.*—In the course of a year we have given thiocyanate to 26 patients. Sixteen of these have been followed for periods varying from two to nine months; they have attained satisfactory blood levels and have cooperated satisfactorily. The remaining 10 are not considered here because (1) a satisfactory blood level was not reached, usually because the patient discontinued visits, or (2) the time interval is

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inadequate to evaluate results. Cooperation has been much more satisfactory since introduction of the micromethod.

The initial dose employed is 0.1 gm. of potassium thiocyanate three times a day. We determine the thiocyanate level in the blood at the end of a week. The dose is then continued or, usually, increased. For example, in one case with the initial dose of 0.3 gm. a day, the level at the end of a week was 4 mg. per 100 c.c. The dose was then increased to 0.6 gm. a day, and at the end of a week the blood level was 8 mg. A final increase to 0.8 gm. a day was followed by a blood level of 10 mg. This we have regarded as optimal. If a blood level of 10 mg. is maintained for two weeks and no appreciable drop in blood pressure occurs, we abandon the medication.

We prefer to give the daily dose in three or four equal fractions rather than in a single dose. If the dose is high, it is well to take it in water to avoid gastric irritation. Aromatic elixir has been a satisfactory vehicle. We have used the potassium salt exclusively, although Barker stated the sodium salt is quite as satisfactory.

Arbitrarily we have defined a successful case as one in which the systolic pressure falls to 170 mm. or lower, with a corresponding decline in diastolic pressure and with associated subjective improvement.

#### *Micromethod for Thiocyanate Determination.—*

##### A. Solutions and materials

1. Ten per cent trichloroacetic acid solution.
  2. Ferric nitrate reagent. Dissolve 50 gm. of crystallized ferric nitrate in 500 c.c. of distilled water. Add 25 c.c. of concentrated nitric acid and make up to 1 liter with distilled water.
  3. Thiocyanate standards. Stock solution. Dissolve about 1 gm. of potassium thiocyanate in 800 c.c. of distilled water. Titrate a 20 c.c. portion of a standard silver nitrate solution (made by dissolving exactly 2.92 gm. of silver nitrate in 1 liter of distilled water) acidified with 5 c.c. of concentrated nitric acid, with the potassium thiocyanate solution, using ferric ammonium sulphate as an indicator. Dilute the thiocyanate solution to a strength equivalent to that of the silver solution volume for volume; it then contains 100 mg. per 100 c.c. Standards may be made up from this by dilution as desired. We employ 10 mg. and 4 mg. per 100 c.c. to check against the ink standards, which will be described later.
  4. Standards of ink. These standards are tedious to make up and are not absolutely necessary because standards of thiocyanate can be set up in small tubes for each working period. However, the ink standards do not fade, or at least have not done so yet, while the thiocyanate standards must be made up fresh each day. "Permanent" standards save at least one-half hour for each working period.
- Yellow\* and red† inks are used. In preparing the ink standards, thiocyanate standards are set up in test tubes, diluting from the stock solution described in Section 3 so as to have strengths per 100 c.c. of 4, 5, 6, 7, 8, 9, 10, 11, 13, and 15 mg. Each solution is then mixed with an equal volume of trichloroacetic acid and one-fifth of the combined volume of ferric nitrate reagent.

The two inks, a few drops at a time, are added slowly to approximately a liter of water in a clear container. The approximate proportion was two parts of the red

\*Indelible yellow ink made by F. Weber and Co., Philadelphia.

†Higgins Brick Red Waterproof Ink.



to one part of the yellow. From time to time a little is taken out in a test tube and compared with the 15 mg. thiocyanate standard. When the colors appear comparable except that the ink is a little deeper (about 10 to 20 per cent), the solutions are compared in a colorimeter, and a reading of the ink in terms of thiocyanate is obtained. A small amount, approximately 50 to 75 c.c., is then diluted to match exactly the thiocyanate standard of 15 mg. A small amount of this, after it is checked in the colorimeter, is sealed in a glass tube such as that to be used in the actual determination. We use tubing with a 4 mm. outside diameter, a 1.5 mm. inside diameter, and a capillarity in ether of 5 mm. Tubes of the ink standard are compared with tubes from the thiocyanate solution. When the match is satisfactory, the remaining tube standards are made up similarly.

5. A number of glass tubes, drawn to a capillary tip at one end, cut off evenly at the other, about 10 cm. long, with measurements for width as given for the standard tubes. The tubes used to collect blood are coated with potassium oxalate (i.e., a solution of 2 per cent potassium oxalate is sucked up, blown out, and the tubes are permitted to dry). The tubes used for the reactions with the plasma are clean.

#### B. Actual Determination:

1. Collect blood in tube containing potassium oxalate. A column of blood from 6 to 7 cm. long is drawn up through the capillary tip, which is then sealed.

2. Centrifuge. Divide the tube with a file at the cell-plasma junction. Transfer the plasma to a clean tube.

3. Measure the length of the plasma column. Add a similar length of trichloroacetic acid. Seal the capillary end. Mix with a wire. Let stand for ten minutes.

4. Centrifuge.

5. Divide the tube at the precipitate-supernatant fluid junction. Transfer the clear supernatant fluid to a clean tube.

6. Add a column of ferric nitrate reagent one-fifth the length of the column of supernatant fluid. Seal the capillary tip. Mix with a wire.

7. Compare, against the colorimeter light, with the standard tubes, using either freshly made up thiocyanate standards as described in paragraph 4 under "Solutions and materials" or the permanent ink standards. When the inks are used, we check them by making up at semiweekly intervals thiocyanate standards of 4 and 10 mg. for comparison. We have found the ink in sets of tubes constant for at least two months.

Certain points in the handling of such tubes are important. In the first step the blood is introduced through the capillary end and sucked up, by a rubber tube and mouthpiece attached to the wide end as for a blood counting pipette. Before sealing the capillary tip the rubber tube is pinched twice, the first time near the glass tube and the second just distal to the first pinch, releasing the first pinch only after the second has been applied. This draws the blood away from the capillary tip, which is then sealed. When breaking the tube to separate the plasma after centrifuging (step 2), the finger must be applied tightly over the open end or the plasma will run out. Transfer of liquid from one tube to another is made by thrusting the capillary tip of the recipient tube into the lumen of the donor tube and tilting both tubes slightly from the horizontal so that the liquid runs into the recipient tube. Before adding a second reagent, as in steps 3 and 6, move the column from the capillary tip to within 1 cm. of the wide end; this is best accomplished by putting a rubber tube on the capillary end and pinching it progressively nearer the tube. When the rubber tube is released, the fluid should flow readily with slight tilting. If it does not, there is usually a bubble in the capillary tip which must be expelled, either by moving the column backward and forward while applying absorbent cotton to the capillary end or by gentle heat. The mark to which the second reagent is

to be added is made with a file and pencil. The finger is placed over the capillary end, the tube is held vertical with the capillary end up, and the open end is thrust deeply into a test tube containing the reagent to be added. Slight movements of the occluding finger then permit the reagent to rise to the mark designated. An air bubble separates the two columns. Both columns are then permitted to move slightly away from the wide end, by tilting, so that there will be no spill over when the capillary end is heated. The capillary tip is then sealed, and the two columns are mixed with a wire. In step 5 it is important to make sure that the precipitate is evenly packed, i.e., that there are no isolated lakes of plasma below the upper level of the precipitate. If such are present, the tube must be stirred and recentrifuged. Otherwise the reading will be too low.

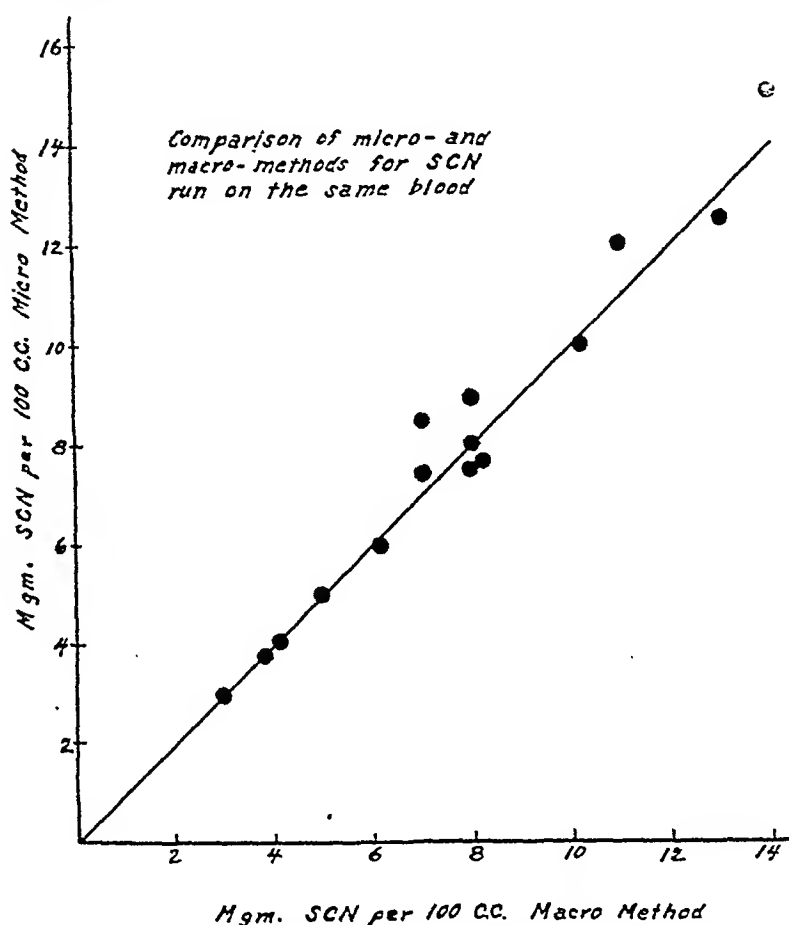


Fig. 1.—Chart showing comparison between blood thiocyanate values obtained in the same patient at the same time by Barker's method and by the micromodification.

## RESULTS

For comparison of readings made at the same time in the same patient by the method of Barker and by our micromodification see Fig. 1. Obviously the micromethod is less exact and can be read only to the nearest milligram. However, for clinical purposes, it is adequate. The level we wish to reach, approximately 10 mg., is 5 mg. below the level at which, according to Barker, mild toxic symptoms occur, 10 mg. below the level of definite toxic symptoms, and 30 mg. or more below a level which is thought to be fatal. Thus the margin of safety is large.

The data concerning the 16 patients adequately treated are listed in Table I. The first ten would be considered good cases according to the

TABLE I

| CASE | SEX | AGE | DURATION<br>(YEARS)<br>HYPERTENSION | BEFORE TREATMENT<br>BLOOD PRESSURE |     | AFTER TREATMENT<br>BLOOD PRESSURE |     | AV.<br>LOWERING | *DURATION<br>(WEEKS)<br>OBSERVATION | SUBJECTIVE<br>LV | DISC<br>CHANGES | RENAL<br>DAMAGE | BLOOD<br>CYANATE<br>LEVEL<br>MG./<br>100 C.C. | DAILY<br>DOSAGE<br>GM. |
|------|-----|-----|-------------------------------------|------------------------------------|-----|-----------------------------------|-----|-----------------|-------------------------------------|------------------|-----------------|-----------------|---|------------------------|
|      |     |     |                                     | SYSTOLIC                           |     | SYSTOLIC                          |     |                 |                                     |                  |                 |                 |   |                        |
|      |     |     |                                     | RANGE                              | AV. | RANGE                             | AV. |                 |                                     |                  |                 |                 |   |                        |
| 1    | F.  | 37  | 3                                   | 178-210                            | 180 | 115-176                           | 150 | 40              | 24                                  | I                | 0               | 0               | 7-13  | 0.6                    |
| 2    | F.  | 43  | 2                                   | 174-230                            | 190 | 150-180                           | 164 | 26              | 5                                   | I                | 0               | 0               | 11  | 0.8                    |
| 3    | F.  | 51  | 3                                   | 175-212                            | 190 | 138-164                           | 150 | 40              | 20                                  | I                | 0               | 0               | 10  | 0.6                    |
| 4    | F.  | 49  | 7                                   | 215-230                            | 220 | 162-168                           | 165 | 55              | 14                                  | I                | 0               | 0               | 8   | 0.6                    |
| 5    | F.  | 33  | 12                                  | 210-238                            | 230 | 168-182                           | 170 | 60              | 10                                  | I                | 0               | 0               | 9   | 0.8                    |
| 6    | F.  | 52  | 4                                   | 225-235                            | 240 | 150-165                           | 160 | 70              | 23                                  | I                | 0               | 0               | 9.5   | 0.8                    |
| 7    | F.  | 43  | 10                                  | 190-220                            | 195 | 150-165                           | 160 | 35              | 39                                  | I                | 0               | 0               | 10  | 0.8                    |
| 8    | M.  | 53  | 1                                   | 200-240                            | 220 | 130-190                           | 165 | 55              | 9                                   | I                | 0               | 0               | 13  | 0.6                    |
| 9    | F.  | 46  | 1                                   | 180-225                            | 215 | 168-174                           | 170 | 45              | 4                                   | I                | 0               | 0               | 10  | 0.8                    |
| 10   | M.  | 34  | 2                                   | 200-220                            | 210 | 165-178                           | 170 | 40              | 7                                   | I                | 0               | 0               | 10  | 1.0                    |
| 11   | F.  | 46  | 7                                   | 200-250                            | 220 | 174-206                           | 190 | 30              | 13                                  | I                | 0               | 0               | 4.8   | 0.4                    |
| 12   | F.  | 70  | 9                                   | 190-250                            | 240 | 194-210                           | 200 | 40              | 16                                  | U                | 0               | 0               | 10-13   | 0.3                    |
| 13   | F.  | 63  | 3                                   | 182-240                            | 220 | 178-184                           | 180 | 40              | 12                                  | I                | 0               | 0               | 8.5   | 0.4                    |
| 14   | F.  | 35  | 8                                   | 200-240                            | 220 | 178-206                           | 182 | 38              | 18                                  | W                | 0               | Sl.             | 11  | 0.4                    |
| 15   | F.  | 40  | 6                                   | 220-275                            | 250 | 228-252                           | 240 | 10              |                                     | U                | 0               | Sl.             | 11  | 0.8                    |
| 16   | F.  | 31  | 5                                   | 220-275                            | 230 | 210-240                           | 230 | 0               |                                     | U                | Sl.             | 0               | 10  | 1.0                    |

\*Duration (weeks) observation refers to the period beginning with the lowering of the blood pressure to 170 or less with a satisfactory blood cyanate level, and ending with the time of writing this article.  
 †Subjectively; I—Improved; U—unchanged; W—worse.

definition previously given. In Cases 11 to 13 the blood pressures were somewhat lowered but not to the desired level, while the patients either felt better or at least were no worse. These cases might be classed as equivocal. Cases 15 and 16 are classed as failures because there was no effect on blood pressure. Case 14 is also considered a failure because, although the blood pressure was lowered somewhat, the patient felt worse.

Patient 7 is charted in detail in Fig. 2. This woman, aged forty-three years, was known to have had a hypertension averaging about 195 mm. systolic since 1927. It had been taken many times by her husband, a physician, but for simplicity the figures charted include only those ob-

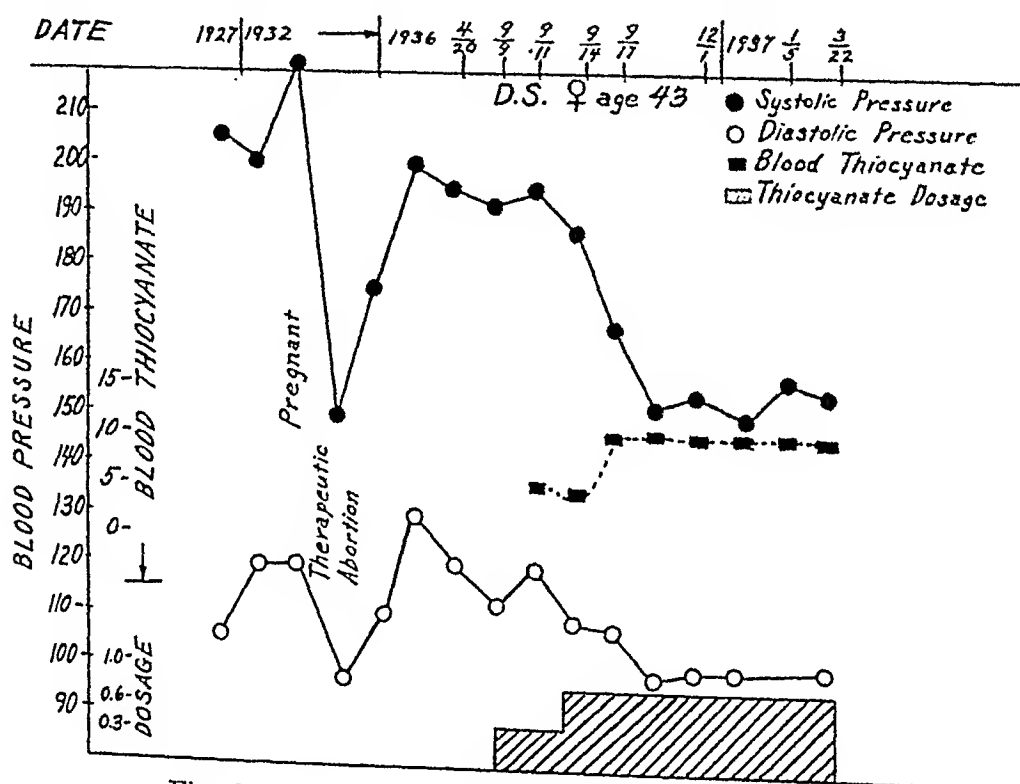


Fig. 2.—Chart of Patient 7. For details see text.

tained on visits to our clinic. Many forms of treatment, including sedatives and endocrine products, had been tried without effect. The only period when the systolic blood pressure reached 150 immediately followed a therapeutic abortion. She had been more or less invalided for years, with recurring headaches and bouts of nausea. On thioeyanate therapy her blood pressure has ranged between 150 and 165 for nine months, and her headaches and attacks of nausea have disappeared. She is leading a normal life.

While analysis of such a small series is of doubtful significance, our results conform with those obtained by Barker. We have had no fatal results and no major complications of any sort. Two patients (Cases 6 and 11) developed a little pruritus with the larger doses. One patient (Case 12) had a mild gastrointestinal upset which may or may not have

been due to the drug. Patient 14 felt worse when her blood pressure was lowered, but no complications were noted.

#### SUMMARY

Thiocyanate was given to 26 patients with hypertension. The dosage was controlled by blood thioeyanate determinations according to the principle of Barker. No fatalities and no major complications occurred. Of the 16 patients adequately treated and controlled, 10 had a good result: i.e., systolic blood pressure fell to 170 or lower, with a corresponding fall in diastolic pressure, and there was subjective improvement. Dosage varied from 0.3 to 1.0 gm. a day. The blood thiocyanate level varied from 8 to 13 mg., though 10 mg. was the level desired. A micromodification of Barker's blood thiocyanate method was devised using standards of ink which seem to be relatively permanent. This method utilizes blood from finger puncture rather than venipuncture and is sufficiently accurate for clinical requirements.

#### REFERENCES

1. Barker, M. H.: The Blood Cyanates in the Treatment of Hypertension, *J. A. M. A.* 106: 762, 1936.
2. Barker, M. H.: The Use of Cyanates in the Treatment of Hypertension, *Wisconsin M. J.* 36: 28, 1937.

# RECIPROCAL RHYTHM IN A PATIENT WITH CONGENITAL HEART DISEASE\*

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**D**URING the study of electrocardiograms showing unusual transitions between normal sinus rhythm, ventricular escape, A-V nodal rhythm, and A-V dissociation,<sup>1</sup> one patient was encountered whose electrocardiograms on several occasions exhibited reciprocal rhythm. As it was possible to observe this patient over a considerable period, and as reciprocal rhythm is a rare condition, at times incorrectly diagnosed,<sup>2</sup> a brief report of this case seemed advisable.

## CASE REPORT

M. S., a twenty-three-year-old hospital employee, was admitted to the Rhode Island Hospital Oct. 15, 1934, complaining of vomiting, diarrhea, and general malaise of one day's duration. He gave a history of previous gastrointestinal upsets following the ingestion of pork or ham, and he had eaten pork for lunch on the day prior to entry. On the day of entry he felt uncomfortable generally and developed progressive nausea and, somewhat later, diarrhea. There were no complaints referable to the cardiovascular system.

*Past History.*—He had always been well. There was no history of rheumatic fever, chorea, or epistaxis. He had never noted or been told of periods of cyanosis. He had noted no dyspnea, and, during the summer prior to admission, had frequently swum over a mile without difficulty. After vigorous exertion he was occasionally conscious of mild palpitation.

*Physical Examination.*—The patient was a very well-developed and well-nourished young white male, lying comfortably in bed. Temperature was 104.6° F.; pulse, 80; and respiration, 25. The significant positive findings were limited to the chest. The heart was definitely enlarged to the left by palpation and percussion. No thrills were felt, but a distinct shock could be felt in the region of the pulmonic valve and along the left sternal border. Upon auscultation this shock was found to be synchronous with a very loud pulmonic second sound. With full inspiration this pulmonic second sound became reduplicated. The only murmur present was a 2 to 3 plus (4 plus = maximum) systolic murmur, loudest along the left sternal border in the third and fourth interspaces. The rhythm was variable, at times being regular and at times exhibiting coupled beats. The coupled beats were more apt to appear during the maintenance of full inspiration. The heart rate varied between 50 and 90 beats a minute, and the blood pressure was 115/60.

*Laboratory Studies.*—Urine studies were negative. The Wassermann test was negative. Microscopic blood studies were normal except for a leukocytosis of 21,000 with 80 per cent polymorphonuclear cells. The stools showed occult blood on one occasion. Subsequent examinations were negative. No ova or parasites were seen.

*Course and Further Studies.*—The temperature rapidly dropped to normal and the gastrointestinal disturbance disappeared in two to three days. After the tempera-

\*From the Heart Station of the Rhode Island Hospital, under the direction of Dr. Frank T. Fulton.

ture dropped, bigeminy occurred less frequently. Orthofluoroscopic studies of the chest showed the heart diameter to be 14.9 cm. and the internal chest diameter to be 25.4 cm. There was definite enlargement of the left ventricle both to the left and posteriorly. No enlargement of the left auricle was detected. There was increased prominence in the region of the pulmonary conus. The cardiac pulsations were slow and vigorous.

The patient was soon discharged from the ward with a diagnosis of acute enteritis and congenital heart disease, probably patent interventricular septum. He has continued in the employ of the hospital, is in excellent health, and has developed no new symptoms or signs (March 15, 1937). Occasional electrocardiograms taken during the past two years have shown, for the most part, S-A rhythm. At times A-V nodal rhythm has occurred, but reciprocal rhythm has not appeared spontaneously in the tracings taken.

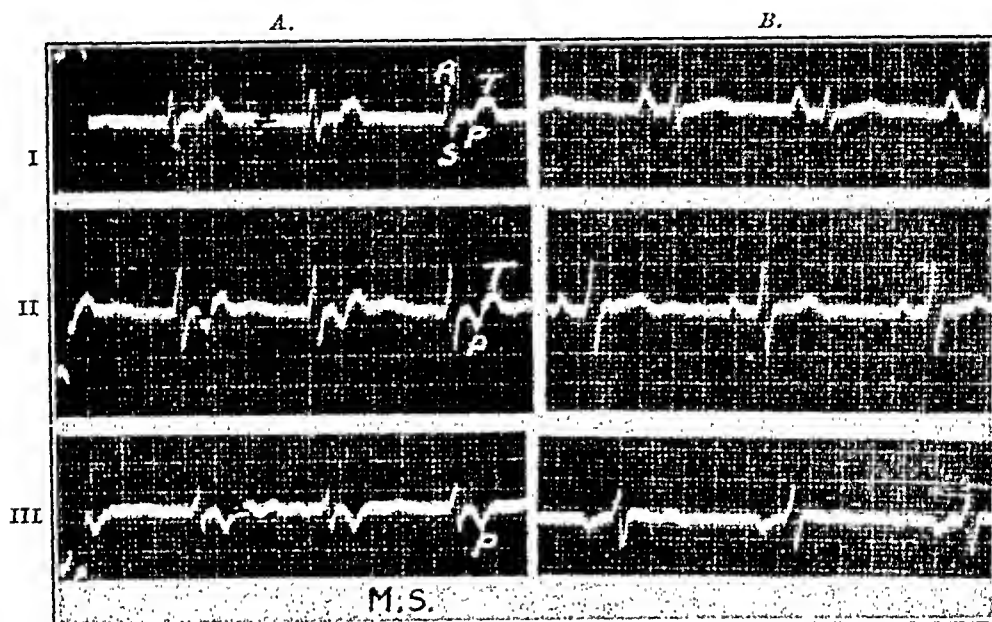


Fig. 1.—Tracing A, at the left, was recorded while the patient was exhibiting uncomplicated A-V nodal rhythm. It was taken Oct. 31, 1934, forty-five minutes after the subcutaneous administration of atropine, grain one-thirtieth. The rate was 70 per minute. Tracing B, at the right, was recorded while the patient was exhibiting uncomplicated S-A rhythm. It was taken Oct. 20, 1934, during bed rest without previous medication. The rate was 55 per minute. In Lead I note the nearly isoelectric P-waves in tracing A and the high P-waves in tracing B.

#### ELECTROCARDIOGRAPHIC STUDIES

Fifty-eight electrocardiograms were taken on this patient under various circumstances, and, of this number, thirteen showed one or more instances of reciprocal rhythm. The remainder were about equally divided in showing S-A and A-V rhythm.

In reviewing the tracings it was noted that the transitions between S-A and A-V rhythm were frequent and would often occur spontaneously. Consequently, it was difficult and often impossible to attribute the presence of any one type of rhythm to any procedure employed or drug administered. The effect or lack of effect of various conditions and drugs is outlined below.

**Fever:** Reciprocal rhythm was frequently present during the short time that the patient's temperature was significantly elevated. Whether this was due to the fever, or to infection or toxemia, we do not know. No subsequent febrile episodes have been present to date.

*Ingestion of Cold Water:* No definite effect was noted.

*Change of Posture:* This involved taking records with the patient sitting up and immediately after lying down. The reverse procedure was also tried. No consistent change was noted.

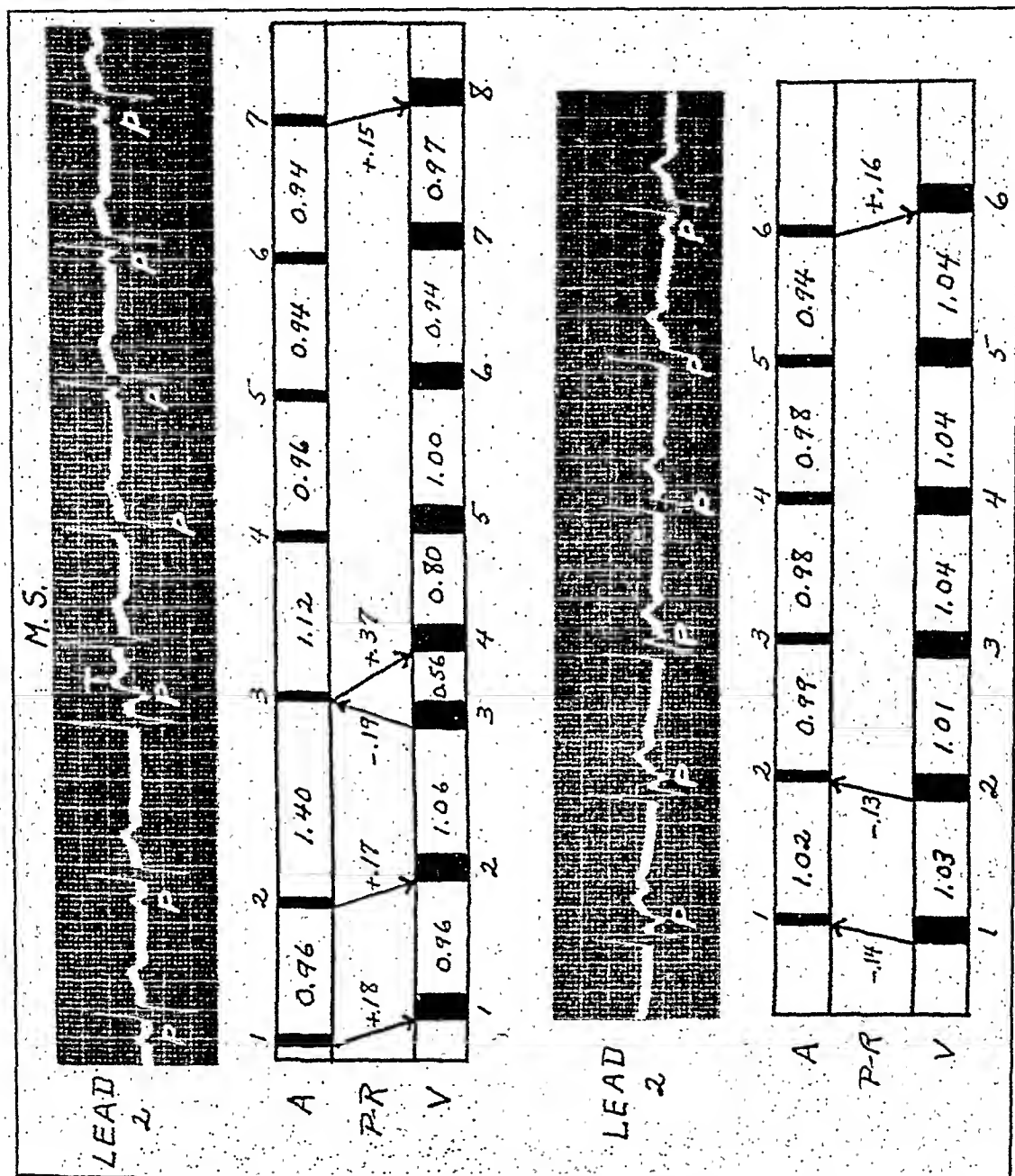


Fig. 2.

Fig. 2.—These two tracings in Lead II show the transitions in rhythm that frequently appeared spontaneously in this patient. The top tracing, taken Oct. 19, 1934, shows the sudden appearance of a reciprocal beat in the midst of S-A rhythm. The bottom tracing, taken Oct. 20, 1934, shows a transition from A-V to S-A rhythm.

The diagrams beneath this and subsequent electrocardiograms are arranged in identical fashion and may be described together. The vertical black bars in the upper strip, marked A, represent the auricular beats and are placed directly beneath the P-waves in the accompanying electrocardiogram. In the middle strip, marked P-R, are recorded, in hundredths of a second, the P-R intervals (preceded by a plus sign) or the R-P intervals (preceded by a minus sign). The arrows in this middle strip indicate the direction of impulse conduction and are only included when it seems probable that a beat has been actually conducted. In the bottom strip, marked V, the heavy vertical bars represent and are placed directly beneath the ventricular beats. The intervals between the auricular and ventricular beats are recorded in hundredths of a second. The auricular and ventricular beats are numbered consecutively in each diagram.



*Carotid Sinus Pressure:* This was tried on each side on several occasions, and no constant effect was elicited.

*Exercise* to the point of mild dyspnea resulted in rhythm of either S-A or A-V origin, at a somewhat increased rate. The ventricular rate (85 per minute) was quite equal to that present when the temperature was elevated and when reciprocal beats were frequent.

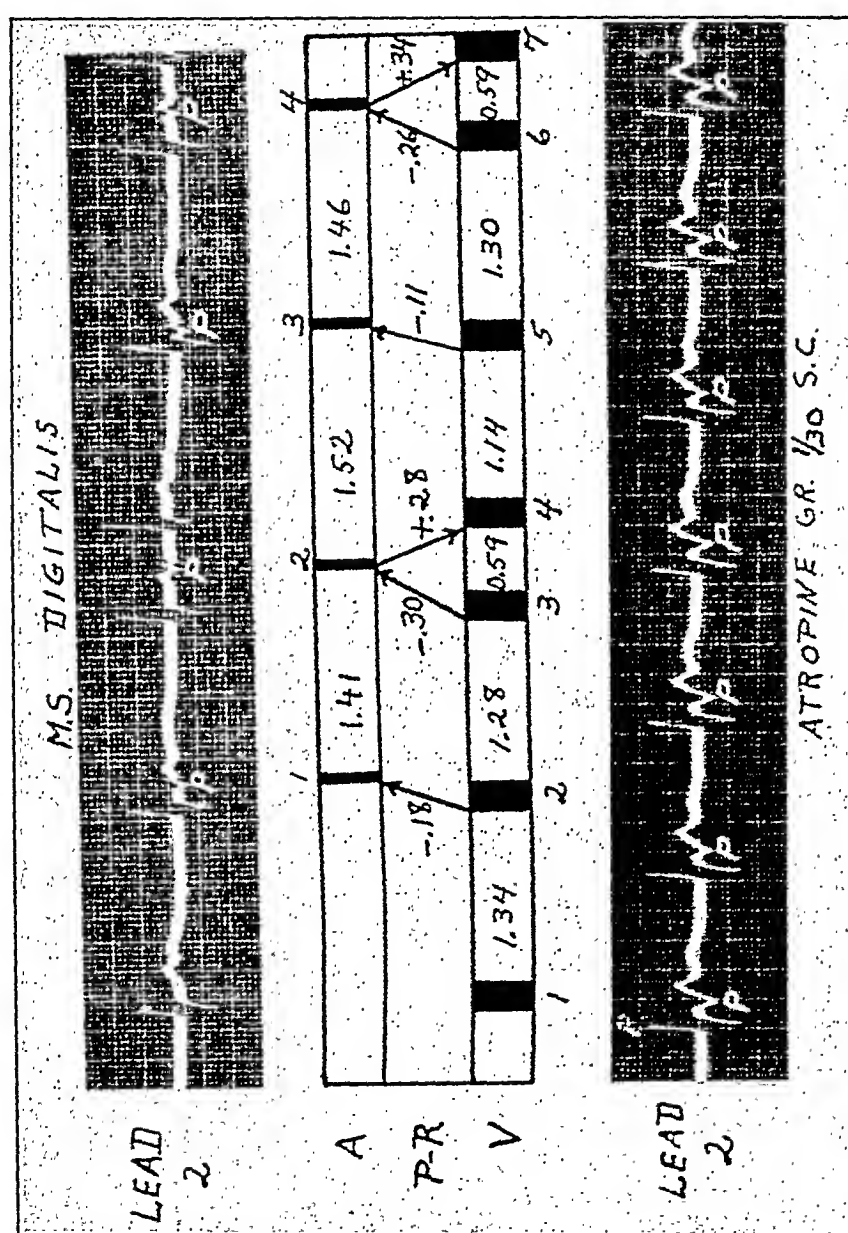


Fig. 3.—Both electrocardiograms were taken in Lead II on Dec. 10, 1934. The top tracing was taken after the administration of large amounts of digitalis over a period of thirty-three days. Several other control tracings on this day showed reciprocal rhythm. The bottom tracing was taken thirty minutes after the subcutaneous administration of atropine, one-thirtieth grain. The reciprocal rhythm was abolished and A-V nodal rhythm appeared. Later, as the effects of the atropine wore off, reciprocal rhythm reappeared.

*Adrenalin:* Twelve minims (1-1000 solution) were injected subcutaneously on one occasion. This raised the rate per minute from 53 to 65 in fifteen minutes. All of several tracings made after the injection showed S-A rhythm. However, the control tracing on this day also showed S-A rhythm, so no convincing evidence is present that this amount of adrenalin had any appreciable effect.

*Forced Deep Respiration:* On several occasions this was tried and almost always resulted in A-V rhythm. Occasionally, especially after a forced expiration, reciprocal rhythm occurred. Except for the administration of digitalis (Fig. 3), temporary

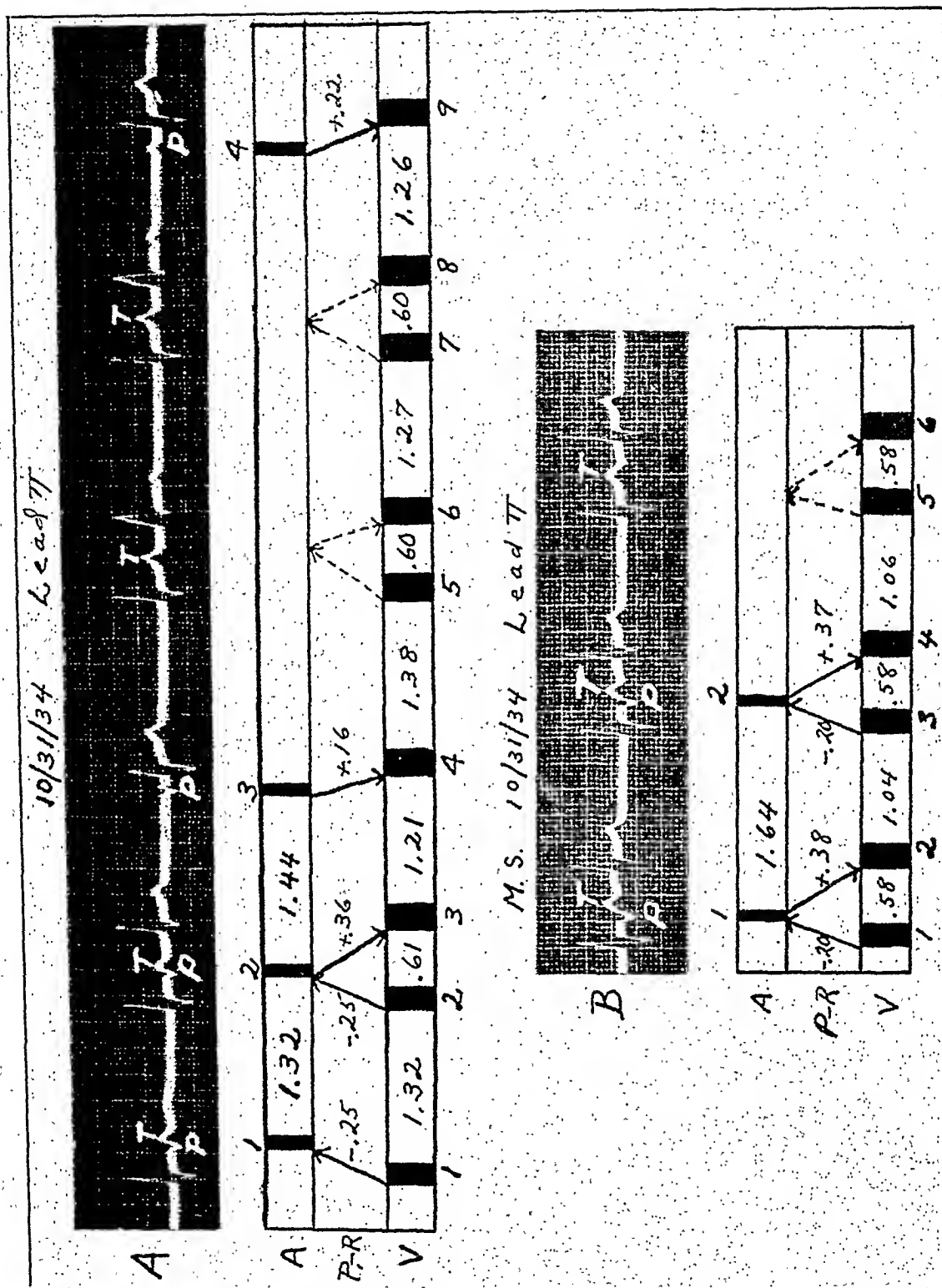


Fig. 4.

Fig. 4.—Both electrocardiograms were taken Oct. 31, 1934, in Lead II. The longer tracing A was a control electrocardiogram taken before the administration of atropine. Note the reciprocal beat (ventricular beats 2 and 3) and later the two couples (ventricular beats 5 and 6, and 7 and 8). In the two latter instances observe the absence of clear evidence of auricular activity between the two beats of the couple, and the slurring of the second ventricular beat in each pair. See discussion in text.

The shorter tracing B was taken twenty minutes after the administration of one-thirtieth grain of atropine subcutaneously, while right carotid sinus pressure was being applied. Here recurring reciprocal beating is present. Note the absence of the P-wave between ventricular beats 5 and 6. In all three couples the interval between the two ventricular beats is constant.

TABLE I

The time relations of the various components of the reciprocal beats observed in Leads II and III. Those observed in Lead I were not included, as the P-waves were often difficult to clearly identify. Note the constancy of the R-R interval, and the variability of the P-R and R-P intervals, observed on Dec. 10, 1934. Also note the variability in the character of the second QRS complex.

| DATE AND LEAD                 | R-R INTERVAL (SECONDS) | R-P INTERVAL (SECONDS) | P-R INTERVAL (SECONDS) | CONDITION OF SECOND QRS |
|-------------------------------|------------------------|------------------------|------------------------|-------------------------|
| 10/16/34                      |                        |                        |                        |                         |
| Lead II                       | 0.57                   | 0.22                   | 0.35                   | R lower, S deeper       |
| Lead II                       | 0.56                   | 0.22                   | 0.34                   | R lower, S deeper       |
| Lead III                      | 0.60                   | 0.20                   | 0.40                   | No change               |
| Lead III                      | 0.58                   | 0.21                   | 0.37                   | No change               |
| 10/19/34                      |                        |                        |                        |                         |
| Lead II                       | 0.56                   | 0.19                   | 0.37                   | R higher, S smaller     |
| 10/31/34                      |                        |                        |                        |                         |
| Lead II                       | 0.64                   | 0.25                   | 0.39                   | Slurred, R higher       |
| Lead II                       | 0.62                   | 0.22                   | 0.40                   | No change               |
| Lead II                       | 0.60                   | 0.24                   | 0.36                   | No change               |
| Lead II                       | 0.60                   | 0.22                   | 0.38                   | No change               |
| Lead II                       | 0.59                   | 0.20                   | 0.39                   | Much slurred            |
| Lead II                       | 0.59                   | 0.28                   | 0.31                   | Much slurred            |
| Lead II                       | 0.60                   | 0.22                   | 0.38                   | No change               |
| Lead II                       | 0.62                   | 0.21                   | 0.41                   | R higher, no S          |
| Lead II                       | 0.62                   | 0.20                   | 0.42                   | R higher, slurred       |
| Lead II                       | 0.61                   | 0.28                   | 0.33                   | No change               |
| Lead II                       | 0.56                   | 0.19                   | 0.37                   | No change               |
| Lead II                       | 0.61                   | 0.25                   | 0.36                   | R higher, S smaller     |
| Lead II                       | 0.58                   | 0.20                   | 0.38                   | R higher, S smaller     |
| Lead II                       | 0.58                   | 0.20                   | 0.38                   | R higher, S smaller     |
| 11/ 1/34                      |                        |                        |                        |                         |
| Lead II                       | 0.64                   | 0.28                   | 0.36                   | Slightly slurred        |
| Lead II                       | 0.64                   | 0.28                   | 0.36                   | Slightly slurred        |
| Lead II                       | 0.63                   | 0.27                   | 0.36                   | Slightly slurred        |
| Lead II                       | 0.61                   | 0.38                   | 0.23                   | S deeper                |
| Lead III                      | 0.60                   | 0.21                   | 0.39                   | Much widened            |
| 12/ 4/34                      |                        |                        |                        |                         |
| Lead II                       | 0.60                   | 0.23                   | 0.37                   | Slightly slurred        |
| 12/ 8/34                      |                        |                        |                        |                         |
| Lead II                       | 0.62                   | 0.26                   | 0.36                   | No change               |
| Lead II                       | 0.66                   | 0.26                   | 0.40                   | No change               |
| Lead III                      | 0.60                   | 0.26                   | 0.34                   | R higher                |
| Lead III                      | 0.61                   | 0.26                   | 0.35                   | R higher                |
| Lead III                      | 0.60                   | 0.22                   | 0.38                   | R higher                |
| Lead III                      | 0.62                   | 0.24                   | 0.38                   | No change               |
| Lead III                      | 0.60                   | 0.28                   | 0.32                   | No change               |
| 12/10/34                      |                        |                        |                        |                         |
| Lead II                       | 0.59                   | 0.30                   | 0.29                   | R higher, S smaller     |
| Lead II                       | 0.60                   | 0.23                   | 0.37                   | R higher, S smaller     |
| Lead II                       | 0.59                   | 0.25                   | 0.34                   | R higher, S smaller     |
| Lead II                       | 0.60                   | 0.30                   | 0.30                   | R higher, S smaller     |
| Lead II                       | 0.60                   | 0.24                   | 0.36                   | R higher, S smaller     |
| Lead II                       | 0.60                   | 0.24                   | 0.36                   | R higher, S smaller     |
| Lead II                       | 0.60                   | 0.25                   | 0.35                   | R higher, S smaller     |
| Lead II                       | 0.59                   | 0.27                   | 0.32                   | R higher, S smaller     |
| Lead II                       | 0.60                   | 0.19                   | 0.41                   | R higher, S smaller     |
| Lead II                       | 0.59                   | 0.26                   | 0.33                   | R higher, S smaller     |
| Lead III                      | 0.60                   | 0.33                   | 0.27                   | R much higher           |
| Lead III                      | 0.60                   | 0.32                   | 0.28                   | R higher                |
| Lead III                      | 0.60                   | 0.28                   | 0.32                   | R higher                |
| Lead III                      | 0.60                   | 0.20                   | 0.40                   | R much slurred          |
| Lead III                      | 0.60                   | 0.28                   | 0.32                   | R higher                |
| Lead III                      | 0.60                   | 0.34                   | 0.26                   | R higher                |
| Maximum difference in figures | 0.10                   | 0.19                   | 0.19                   |                         |

maintenance of full expiration seemed to be the procedure most likely to result in reciprocal rhythm. Wilson<sup>3</sup> has noted instances of a shift of the pacemaker from the S-A to the A-V node with deep respiration.

*Digitalis:* Four-and-one-half grains a day were given by mouth for twenty-one days. At the end of this time there were no discernible effects by electrocardiogram, and no symptoms. Consequently, the daily dose was raised to six grains, and this was continued for another twelve days. There were still no toxic symptoms, and the patient's appetite remained excellent. However, at this time, the electrocardiogram showed frequently recurring examples of reciprocal rhythm (Fig. 3). Previous electrocardiograms taken during the period of digitalis administration had shown, for the most part, A-V nodal rhythm. White,<sup>4</sup> Dock,<sup>5</sup> and Blumgart and Gargill<sup>6</sup> have observed the more frequent occurrence of reciprocal rhythm after digitalization.

*Atropine:* This was administered subcutaneously in one-thirtieth grain doses on two occasions, once before giving digitalis and once at the end of the experiment with digitalis. In the first instance, the control tracing showed transitions between S-A and A-V nodal rhythm. Tracings were taken 20 minutes, 45 minutes, 85 minutes, 4½ hours and 24 hours after the injection of atropine. The first three of these showed A-V nodal rhythm throughout, with a moderate increase in the ventricular rate. The last two tracings, taken when the symptomatic effects of atropine had worn off, were very similar to the control tracing. No consistent tendency to reciprocal rhythm was shown at any time. Jones and White<sup>7</sup> noted a similar lack of effect of atropine in changing A-V rhythm. Wilson<sup>8</sup> has pointed out the tendency of atropine, especially soon after its administration, to convert S-A into A-V rhythm. Bishop,<sup>9</sup> and Dock,<sup>5</sup> however, observed a change from A-V to reciprocal rhythm, following the administration of atropine.

The effect of atropine after digitalis administration was more striking. Tracings were taken 15, 17, and 30 minutes after injection. In all three tracings only A-V nodal rhythm appeared, and the previously observed tendency toward reciprocal rhythm had entirely disappeared (Fig. 3). White,<sup>4</sup> and Blumgart and Gargill<sup>6</sup> have observed the shortening by atropine of R-P intervals previously lengthened by digitalis.

A study of the time relations of the various components of reciprocal rhythm is recorded in Table I. It is readily seen that the interval between the two ventricular beats of a couple is fairly constant throughout. The R-P and P-R intervals, however, show greater variation. Moreover, the length of the R-P interval does not appear to be the sole determining factor in the appearance of reciprocal rhythm. In general, reciprocal rhythm does occur with the longer R-P intervals. However, in some tracings, R-P intervals not followed by reciprocal beats are as long as, or longer than, R-P intervals followed by typical reciprocal beats. The second QRS of a couple often differs somewhat from the first. It may show slurring of greater or less degree, and the relative amplitude of the R- or S-waves may be distinctly different from that seen in the first QRS complex.

#### DISCUSSION

It is not our purpose to enter into a detailed discussion of the mechanism of reciprocal rhythm, as this has been done previously by others<sup>4-6, 10-13</sup> and we have nothing to add. One point in Figure 4B seems worthy of further comment, as it illustrates an observation that we have not encountered in the literature on this subject. It may be noted that the first two groups of coupled beats in this tracing have a definite inverted auricular wave between the two beats of the couple—as is usual in reciprocal rhythm. However, between the beats of the last couple

(ventricular beats 5 and 6) there is no definite evidence of any auricular activity. In spite of this, the interval between the ventricular beats remains the same as in the previous couples (0.58 second). This we take to be suggestive evidence that an impulse may travel up the A-V node or bundle *without* entering the auricle, and return by the same or a slightly different pathway to result in a ventricular response, after an interval equal to that taken by similar impulses that do activate the auricles. This would thus seem to be evidence that auricular systole is not necessary for the occurrence of the second ventricular beat in reciprocal rhythm.

Coupled beats similar to the last one illustrated in Fig. 4B were observed on two other occasions and are shown in Fig. 4A (ventricular beats 5 and 6, 7 and 8). There are two differences to be observed, however. QRS complexes 6 and 8 are considerably slurred, and the T-waves within the couples are more pointed than those seen elsewhere in the tracing. The widened QRS complexes indicate that the impulse has spread through the ventricles differently than in the ordinary beats. However, this point would not by itself militate against a diagnosis of reciprocal rhythm, as we have several otherwise typical instances of reciprocal beating in which the second beat of the couple shows marked slurring. Dock,<sup>5</sup> and Blumgart and Gargill<sup>6</sup> have also observed slurring of the second QRS complex in reciprocal rhythm. The unusual shape of the T-waves indicates the possibility of upright P-waves of S-A origin being buried within them. However, here again, the intervals between the beats of the two couples are practically identical with the interval between the beats of a typical example of reciprocal rhythm shown in the first part of the tracing (ventricular beats 2 and 3). This would suggest that the mechanism of all three couples is much the same. Thus, we believe, the evidence is suggestive that an impulse may travel from the ventricles back to the auricles and return to the ventricles without resulting in an auricular beat. However, further study is necessary to conclusively prove or disprove this point.

#### SUMMARY AND CONCLUSIONS

A case of congenital heart disease with probable patent interventricular septum is presented. Electrocardiograms frequently showed reciprocal rhythm.

During the patient's initial febrile episode, reciprocal rhythm appeared spontaneously on several occasions. Of various experimental procedures tried, only forced respiration and the administration of large amounts of digitalis seemed effective in initiating this type of rhythm. Atropine abolished the effect produced by digitalis and resulted in A-V nodal rhythm.

In the reciprocal rhythm shown by our patient, the second ventricular beat followed the first after a fairly constant interval. The R-P and P-R intervals of the intervening auricular beats were more variable.

Evidence is presented suggesting that reciprocal beats may occur without the presence of a preceding auricular beat.

## REFERENCES

1. Cutts, F. B.: The Transitions Between Normal Sinus Rhythm, Ventricular Escape, A-V Nodal Rhythm, and A-V Dissociation, *AM. HEART J.* 13: 451, 1937.
2. Zeisler, E. B.: A-V Dissociation, *J. Lab. and Clin. Med.* 18: 225, 1932.
3. Wilson, F. N.: Three Cases Showing Changes in the Location of the Cardiac Pacemaker Associated With Respiration, *Arch. Int. Med.* 16: 86, 1915.
4. White, P. D.: A Study of Atrioventricular Rhythm Following Auricular Flutter, *Arch. Int. Med.* 16: 517, 1915.
5. Dock, W.: The Reciprocal Rhythm, *Arch. Int. Med.* 41: 745, 1928.
6. Blumgart, H. L., and Gargill, S. L.: Reciprocal Beating of the Heart; An Electrocardiographic and Pharmacological Study, *AM. HEART J.* 5: 424, 1930.
7. Jones, T. D., and White, P. D.: Atrioventricular Nodal Rhythm; Report of Two Cases Exhibiting Bigeminy, *AM. HEART J.* 2: 266, 1927.
8. Wilson, F. N.: The Production of Atrioventricular Rhythm in Man After the Administration of Atropine, *Arch. Int. Med.* 16: 989, 1915.
9. Bishop, L. F.: Specific Action of Atropine in Relieving Certain Irregularities of Heart Beat, *J. A. M. A.* 77: 31, 1921.
10. Wolferth, C. C., and McMillan, T. M.: Observations on the Mechanism of Relatively Short Intervals in Ventriculoauricular and Auriculoventricular Sequential Beats During High-Grade Heart-Block, *AM. HEART J.* 4: 521, 1929.
11. White, P. D.: The Bigeminal Pulse in Atrioventricular Rhythm, *Arch. Int. Med.* 28: 213, 1921.
12. Drury, A. N.: Paroxysmal Tachycardia of A-V Nodal Origin, Exhibiting Retrograde Heart-Block and Reciprocal Rhythm, *Heart* 11: 405, 1924.
13. Luten, D., and Jensen, J.: Ventricular Bigeminy in Atrioventricular Rhythm, *AM. HEART J.* 7: 593, 1932.

# STUDIES OF THE COLLATERAL CIRCULATION FOLLOWING EXPERIMENTAL VASCULAR OCCLUSION\*

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THIS investigation was undertaken with the purpose of producing vascular obstruction in the rabbit—to follow from inception to termination the changes that occur—and to evaluate the factors which influence the development and effectiveness of the collateral circulation. A major portion of the study was devoted to the effect of passive vascular exercise.

## PROCEDURE

The ears of mature rabbits were selected because they, like the extremities, are peripheral organs; and because temperature and color changes of the skin could be readily correlated with changes in the caliber of the vascular tree.

Groups of animals were prepared and then treated according to the following schema: (Table I) :

TABLE I

| GROUP | NO. OF RABBITS                              | PASSIVE VASCULAR EXERCISE   | REMARKS  |
|-------|---|---|--|
| I     | 1 normal control<br>1 ligated control       | Pressures: -30 -20<br>-50 -30<br>Cycle: 30" negative<br>10" positive<br>Rx: 15 to 60 min. | Surface and vascular reactions.  |
| II    | 1 ligated control<br>3 ligated test animals | Pressures: -30 -40; -20<br>3 wk. treatment ½ hr. to<br>1 hr. daily                        | Ligation of main vessels at base of ear only.  |
| III   | 1 ligated control<br>3 ligated test animals | Pressures: -30 -10<br>1 hr. daily for 1 mo.   | Ligation of main vessels at base of ear and also at level of middle of ear.  |
| IV    | 1 ligated control<br>2 ligated test animals | Pressures: -30 -10<br>1 hr. daily 2 mo. treatment   | Very complete ligation of main branches at several levels.<br>Development of gangrene on treated side 1 to 2 weeks after start of treatment. |

The individual animals presented the normal (ear) circulatory pattern for rabbits, i.e., a central artery and two marginal branches, one medial and one lateral. These ramify profusely and anastomose very freely so that an intimate vascular network is formed. The veins closely parallel the arterial side of this system.

*Preparation of Animals.*—A through-and-through mass ligation was made at the base of the ear around each of the main vessels until they ceased to pulsate. The animals were anesthetized with ether prior to the operation. A week was permitted

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to elapse to permit thrombosis and organization of the thrombus, as well as subsidence in the local reaction to the ligatures.

*Methods of Study.*—1. Surface reactions, i.e., changes in skin temperature, color and tissue necrosis, were observed daily.

2. Vascular changes were recorded by means of photographic and arteriographic studies. For the former, the animal was placed in a box with a sliding cover so that only its head projected above the surface. Back of the ears and supporting them was a thick rectangular glass jar filled with water. The ears were kept together by a small piece of adhesive plaster. With illumination coming through the glass jar from behind, the vascular tree was shown up very effectively, and the heating effects eliminated. The usual photographic factors of exposure time, aperture, distance of object from lens, and illumination were kept constant. For the arteriographic studies, the animal was anesthetized with ether. A rubber tourniquet was placed tightly around the abdomen just below the costal cage to cut off the blood supply to the lower half of the body. An intracardiac injection of 3 c.c. of thorotrast was made under sterile precautions, and x-ray films of the ears were taken. The anesthesia and the intracardiac injection could be repeated within a few days without danger. Many of the animals received as many as 5 or 6 such treatments.

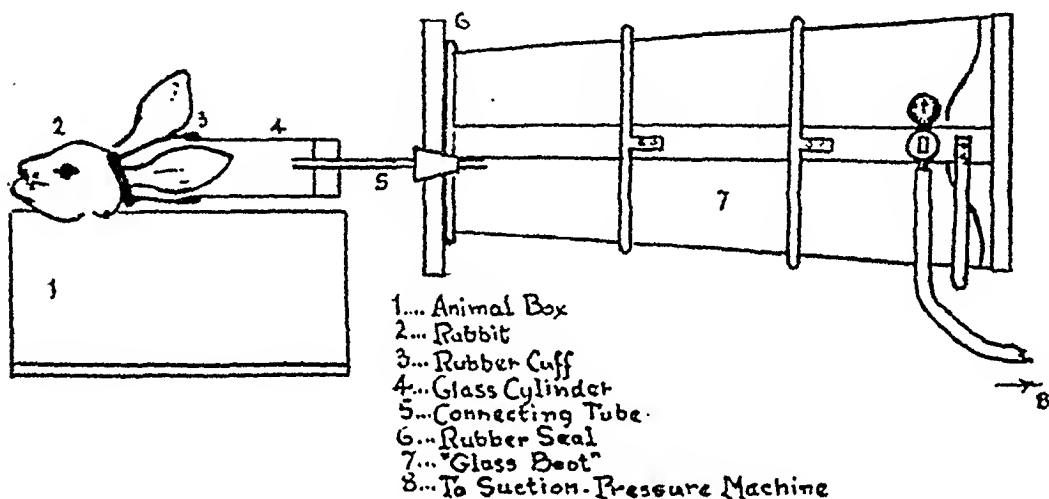


Fig. 1.—Apparatus and position of animal during treatment.

At the termination of each experiment the animals were killed with ether, and a dissection of the neck organ was made to isolate the carotid arteries. These were injected with a solution of thorad (1:1 dilution) to which had been added a few drops of methylene blue, the latter to show when filling of the arterial tree had been completed.

Treatment by passive vascular exercise had to be adapted to the experimental animal. Fig. 1 illustrates the setup. A rubber cuff was placed loosely over the ear of the animal so that the soft rubber sponge base rested snugly against the side of the skull. Compression of the vessels mechanically by the cuff was therefore eliminated. A rubber cork was inserted into the external ear so that pressure changes would not be communicated directly to the internal ear. The cuff was attached to a glass cylinder which in turn was connected to the "boot" by means of a piece of glass tubing.

#### OBSERVATIONS

The ears of a rabbit are a very sensitive indicator of the bodily reactions due to internal and external stimuli. They may droop or be erected instantly, and a process of alternate blanching and flushing goes on constantly for variable intervals. When a normal ear is sub-



jected to passive vascular treatment ( $-30$   $-10$  mm. Hg) for a half hour or longer it becomes definitely cyanotic and is cold to the touch. The untreated ear does not become cyanotic and remains warmer than its treated mate. Increasing the pressure to  $-80$   $-20$  mm. Hg produces a proportional increase in the intensity of the cyanosis and the coldness of the ear. The higher the initial pressure the more rapidly are these changes produced. When treatment is stopped, the color and skin temperature of the ear return very quickly to normal within a few minutes. When ears of ligated animals are subjected to the same treatment, the surface changes in general are similar to those above.\* However, there is a quantitative difference—the cyanosis is more intense—a definite blue or even a slate gray. In addition, the return of the

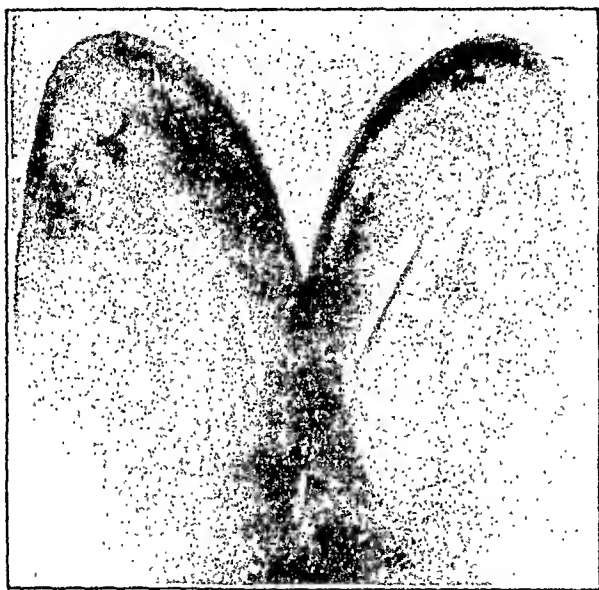


Fig. 2.—Intense cyanosis of treated ear. Also notice blurring of the larger vessels and sparseness of smaller branches.

treated ear to its resting state may take from fifteen minutes to several hours. Cyanosis is last to disappear; the return of the skin temperature is more rapid (Fig. 2).

Immediately after the ligation of the main vascular trunks, the ear becomes cold, white, and lifeless. Within a few days it begins to return to the normal state. Although there are no longer any pulsating vessels, the ear feels warm and flushes as readily as it does normally. The large vessels are definitely narrowed but there is present a marked increase in the number of small collateral branches. This is best exemplified by the following arteriograms: Figs. 3 and 4 on a normal control, Figs. 5 and 6 on a ligated control. In the former, the vascular network follows a definite pattern; branching and sub-branching occur regularly and the vessels themselves are of uniform caliber and smooth

\*In the illustrations, the treated ear will always be found to the left.



Fig. 3.—Arteriogram (in vitro) of a normal control. Vessels are smooth in outline and subdivisions occur regularly.

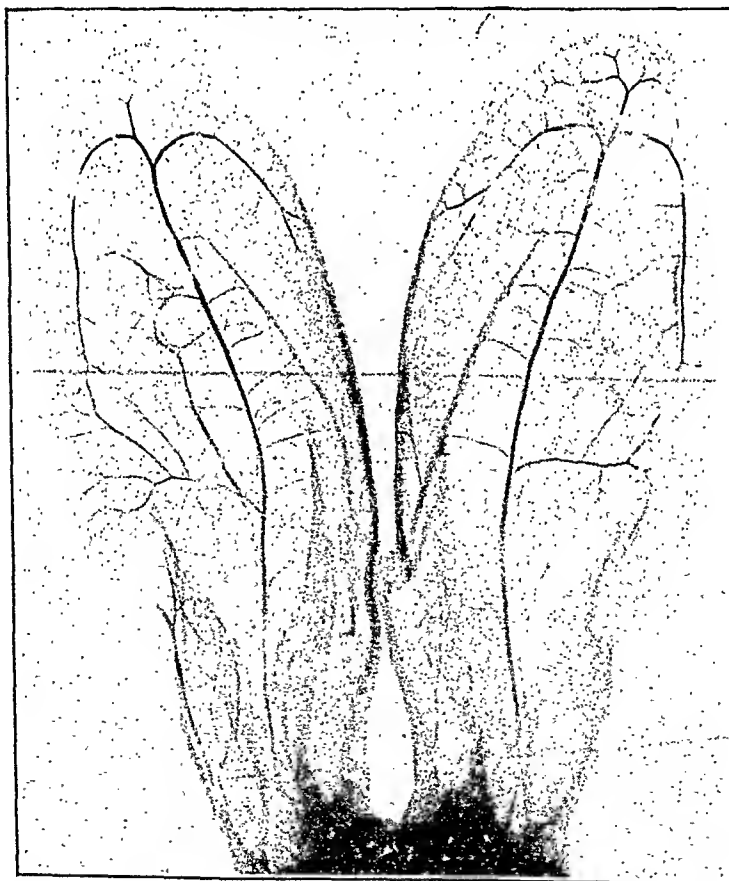


Fig. 4.—Arteriogram (post mortem) of a normal control. Sub-branching more clearly visualized.

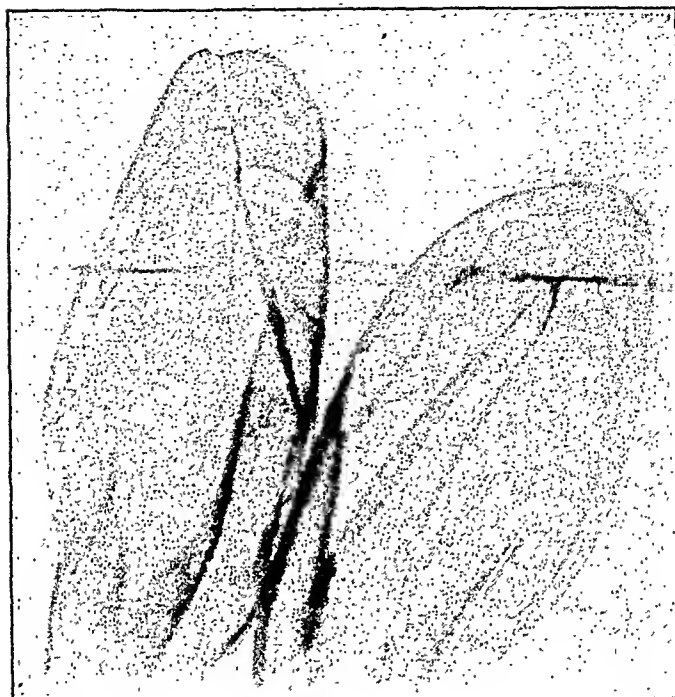


Fig. 5.—Arteriogram (in vitro) of a ligated control. Marked increase in number of collateral vessels.



Fig. 6.—Arteriogram (post mortem) of a ligated control. Notice tortuosity, aimless ramifications, and irregular outline of the collateral vessels—also the bridging of the vascular obstruction by groups of small branches.



Fig. 7.—Arteriogram of ligated test animal. No vessels are visible on the treated side. Those on the untreated side are markedly narrowed, and but few of the smaller vessels are visible.



Fig. 8.—Ears of the same animal after exposure to a radiant lamp for five minutes. Vessels are beginning to appear on the treated side although they are still narrowed and very few collaterals are seen. Notice the marked dilatation on the untreated side and the increase in vascular branching.

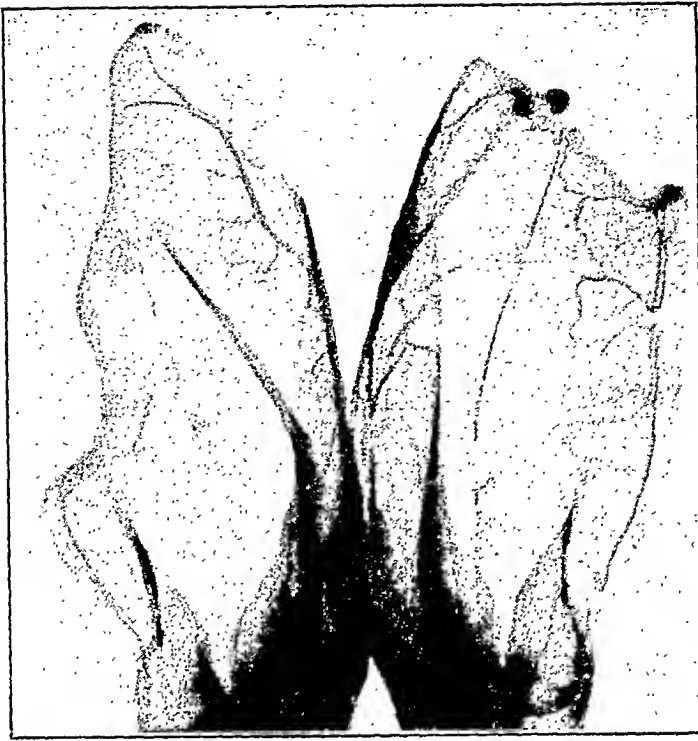


Fig. 9.—Arteriogram (in vitro) of a rabbit treated for several weeks by passive vascular exercise. The treated ear shows extensive necrosis and very few vessels. The untreated side shows a similar condition but to a lesser degree.



Fig. 10.—Arteriogram (post mortem) of the same rabbit. The collateral circulation is quite extensive and approximately equal on treated and untreated sides. In spite of this, necrosis has taken place in both ears.

outline. In the latter, the vessels are tortuous, ramify seemingly aimlessly and are markedly increased in number. This, as has been shown by Allen and Camp,<sup>1</sup> is characteristic of collateral circulation.

When the ligated ear is subjected to passive vascular exercise, several important changes are seen in the arteriographic plates. There is either no filling or only incomplete filling with thorotrast on the treated side. In other words, the lumina of the vessels are so narrowed that the injected material is unable to pass through. This is possibly the result of a vasospasm and may last for a period of several hours. As a matter of fact, even the other ear in the same animal exhibits a certain amount of narrowing of the vascular tree and a sparsity of collateral vessels. These changes may also be due to vasospasm, in all probability a reflex response (Fig. 7). The spasm or closure of the arteries can be overcome to a certain extent by the application of radiant heat just prior to arteriography. Fig. 8 shows this. Although the vessels on the treated side are still narrow and spastic and the collateral circulation still very sparse, yet the lumina have dilated sufficiently to admit the thorotrast. The vessels in the control ear in the same animal are widely dilated, very broad in caliber, and there is an abundance of secondary branches.

In the last group of animals which we subjected to ligation at different levels, we produced closure of the large vessels for almost three-quarters of their length. This meant that extensive collateral circulation would be needed to keep the ear alive. In the first rabbit, eight days after the start of passive vascular exercise and two weeks after ligation, the treated ear began to show an area of necrosis at the tip. Treatment was continued, however, and the area of necrosis became more extensive and finally began to involve the tip of the other ear. In the other test rabbit a similar condition began to appear in the treated ear about fifteen days after treatment, and then in the other and untreated ear about one week later. The control animal, which was also ligated in the same way but received no treatment, exhibited no such changes throughout the experiment. The gangrene kept spreading in the test animals in spite of treatment (Figs. 9 and 10). Post-mortem arteriography showed extensive collateral circulation present in both ears, both on the treated and on the untreated sides.

#### DISCUSSION AND SUMMARY

In our rabbits, simple ligation of the ear vessels proved to be a potent enough stimulus for the development of collateral circulation. Arteriographic studies on the living animal show that extensive branching occurs within a few days. In the human being an analogous condition occurs after acute closure due either to thrombosis or embolism of a large artery. If the collateral circulation develops with sufficient rapidity and to sufficient extent, the tissue involved will be saved. This

occurs with some frequency even without therapy, and makes one feel a trifle skeptical of the brilliant therapeutic results first recorded with suction-pressure treatment. As a matter of fact, the literature in the past year is of a rather equivocal nature, some authorities going so far as to state that passive vascular exercise will "not produce results which have not been produced by simpler methods," and that "when good results do not follow other measures, passive vascular exercise is usually valueless."<sup>2, 3</sup>

In these experiments, which of course were done on rabbits and not on human beings, we can say with certainty that passive vascular exercise is not only superfluous, but harmful. It produces cyanosis and vasospasm which persist for hours; and as treatment is continued, the constant deprivation of the tissues of their blood produces an anoxemia which results in necrosis. It must be emphasized that this sequence of events progresses rapidly in spite of treatment and in face of an abundance of collateral vessels.

NOTE.—I wish to thank Dr. Karl Harpader, attending physical therapist to the Montefiore Hospital, whose guidance and assistance made possible these experiments.

#### REFERENCES

1. Allen, E. V., and Camp, J. D.: Arteriography, *J. A. M. A.* 104: 8, 1935.
2. Wilson, H., and Roome, N. W.: Passive Vascular Exercise: Observations on Its Value in the Treatment of Peripheral Vascular Diseases, *J. A. M. A.* 106: 22, 1936.
3. Allen, E. V., and Brown, G. E.: Intermittent Pressure and Suction in the Treatment of Chronic Occlusive Arterial Disease, *J. A. M. A.* 105: 25, 1935.

# COMPLETE AURICULOVENTRICULAR BLOCK AND AURICULAR FLUTTER WITH OBSERVATIONS OF THE EFFECT OF QUINIDINE SULFATE\*

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COMPLETE auriculoventricular block occurs frequently but it is not often associated with auricular flutter. A search of the literature reveals only 29 authentic cases. The comparative rarity of this condition and the observation of some unusual findings following treatment with quinidine sulfate are the reasons for this report.

The first reliable description of A-V dissociation accompanied by auricular flutter, was made by Jolly and Ritchie<sup>1</sup> in 1911; electrocardiograms and venous pulse tracings were shown. Hertz and Goodhart<sup>2</sup> in 1909 reported a young girl with auricular flutter in whom the ventricular rate fell to 44, after digitalis was administered; no electrocardiograms were made. Keating and Hajek<sup>7</sup> made the first reports in this country. Subsequently, Willius,<sup>11</sup> Strauss,<sup>12</sup> Gager,<sup>17</sup> and Parsonnet and Parent<sup>20</sup> published similar cases. Recently Routier<sup>26</sup> described two cases and summarized those previously recorded.

A survey of these cases (Table I) suggests classification into three types: (1) auricular flutter developing complete block after digitalis; (2) complete block developing flutter when given atropine, digitalis, and in one case after the advent of hyperthyroidism; and (3) the spontaneous occurrence of block and flutter. Our patient was of the last type and probably was first afflicted with heart-block which was subsequently complicated by auricular flutter for no apparent reason.

Only four of the 29 cases reported occurred in females, a somewhat smaller percentage than is found in heart-block alone. The ages varied between thirteen and seventy-four years, with 66 per cent in the sixth and seventh decades. The etiological factors were those characteristic of uncomplicated A-V block, namely, arteriosclerosis and coronary disease in most instances, with three cases of syphilitic heart disease and one each of rheumatic heart disease, congenital heart disease, and thyrotoxicosis. Of the 29 cases, in only eight was the auricular flutter rhythm restored to sinus control, five with quinidine, two with digitalis, and one following thyroidectomy. Quinidine failed to restore the sinus auricular control in one case where it was tried. A summary of the published cases is given in Table I.

\*From the Department of Medicine, New York Post-Graduate Medical School and Hospital.



TABLE I  
SUMMARY OF REPORTED CASES OF COMBINED COMPLETE HEART-BLOCK AND ATRICULAR FLUTTER

| AUTHOR                      | SEX | AGE | AURICULAR | VENTRICULAR | SIGNS   | ELECTROCARDIOGRAM                                   | REMARKS  |
|-----------------------------|-----|-----|-----------|-------------|---|---|--|
| Jolly and Ritchie, 1910     | M   | 61  | 273       | 35          |   | Flutter seen Leads II and III. Left axis deviation  | Syncope five yr., A-V 60/31. Flutter after atropine. Persisted.  |
| Hay, 1913                   | M   | 62  | 260       | 31          | Systolic at apex, B.P. 170/90                 | Electrocardiogram—venous tracing                    | Flutter 10 yr., irregular ventricular rate, 87; after digitalis ventricular, 31 with persistent flutter.                       |
| Douzelot and Pezzi, 1914    | M   | 62  | 300       | 37          | B.P. 170/100; sharp first tone at aortic area | Flutter seen Leads II and III                       | Slow pulse two yr. Syncope one yr.   |
| Martinez, 1916              | M   | 52  | 150       | 40          | Cardiac insufficiency                         | No electrocardiogram; diagnosis by cardiogram       | Cardiorenal with adhesive pericarditis.  |
| Case 4                      | M   | 37  | 250       | 30          | Cyanosis, ascites, systolic at apex           | Diagnosis by cardiogram. Electrocardiogram not good | Cardiac insufficiency for five mo. Autopsy; septal defect with sclerosis of bundle of His.                                     |
| Case 5                      | M   | 13  | 135       | 34          | Cyanosis—systolic at apex                     | No electrocardiogram; flutter on cardiogram         | Three mo. of syncope before death. Autopsy; degeneration of myocardium and bundle of His.                                      |
| Case 12                     | M   | 68  | 250       | 40          | B.P. 285/125; systolic at apex                | No electrocardiogram. Venous tracing                | Bradycardia—auricular 70, ventricular 35; flutter developed for eighteen mo. without symptoms after digitalis.                 |
| Gottling, Vinis, 1920       | M   | 42  | 225       | 25          | Aortic insufficiency, B.P. 140/50             | Flutter seen Lead II. At so bundle-branch block     | Syncope for five mo. Atropine no effect. Adrenalin increased ventricular to 120.   |
| Arrillaga and Waldorf, 1921 | F   | 53  | 360       | 30          |   | Flutter shown Lead II                               | Syncope, tachycardia then flutter with A-V block. Later sinus auricular rhythm and finally alternate flutter and fibrillation. |

TABLE I—Cont'd

|                             |   |    |     |    |  |  |  |   |  |
|-----------------------------|---|----|-----|----|--|--|--|---|--|
| Gallemaerts, 1923           | M | 62 |     |    |  |  | Coronary occlusion                           | Flutter seen Lead II                              | Quinidine restored sinus rhythm.   |
| Wiltshire, 1923             | M | 63 | 240 | 50 |  |  |  |   | 80 syncopal attacks daily auricular rate 100; ventricular 22, then ventricular pauses with auricular rate 160-240. |
| Hall, 1924                  | M | 62 | 250 | 42 |  |  | Bundle-branch block                          | Flutter with complete A-V block                   | Syncope for several years. Then developed flutter.   |
| Willius, 1927               | M | 50 | 236 | 36 |  |  | B.P. 160/95; arteriosclerosis; heart disease | Flutter Leads II and III. Left axis deviation     | Pulse slow five yr., then developed flutter. No improvement on quinidine.  |
| Henderson and Rennie, 1927  | M | 73 | 283 | 32 |  |  | B.P. 165/80; no syphilis                     | Flutter in Leads II and III. Left axis deviation. | No improvement with atropine; died three mo.   |
| Strauss, 1927               | M | 39 | 340 | 42 |  |  | B.P. 135/70-96/60; thyroid adenoma           | Flutter in all leads                              | Complete block. Developed hyperthyroidism and flutter; restoration of auricular sinus rhythm after thyroidectomy.  |
| Parkinson and Bedford, 1927 | M | 74 | 270 | 35 |  |  | Myocarditis. Systolic at apex                | No electrocardiogram. Flutter on phlebogram       | Digitalis produced auricular fibrillation then restoration of sinus rhythm with persistent block.                  |
| Lian and Viau, 1930         | M | 51 | 272 | 36 |  |  | Syphilis. A-V block for 25 years             | Flutter in Leads II and III                       | Digitalis restored sinus auricular control and A-V block persisted.  |
| Guger, 1931                 | M | 70 | 274 | 44 |  |  | Arteriosclerotic; B.P. 122/78                | Flutter Leads II and III. Left axis deviation     | No response to digitalis; quinidine gr. 6 restored sinus rhythm with first stage A-V block.                        |
| Bosco and Vega, 1931        | M | 66 | 260 | 30 |  |  | B.P. 180/120; cardiac insufficiency          | Flutter Leads II and III                          | Flutter for two yr.  |
| Ramos, 1932                 | M | 40 | 300 | 30 |  |  | B.P. 120/50; cardiac insufficiency           | Flutter Leads II and III. Bundle-branch block     | Cardiac insufficiency for two yr. Autopsy: lesions of both bundles.  |

TABLE I—Continued

| AUTHOR                                   | SEX | AGE | AURIC-<br>ULAR | VENTRIC-<br>ULAR | SIGNS  | ELECTROCARDIOGRAM   | REMARKS  |
|--|-----|-----|----------------|------------------|--|---|--|
| Parsonnet and<br>Parent, 1933            | M   | 60  | 230<br>340     | 38               | B.P. 150/60; coronary<br>occlusion                             | Flutter Leads II and III.<br>Left axis deviation, and<br>later, right | Coronary occlusion three mo. previ-<br>ous; slow pulse some years; car-<br>cinoma of abdomen.                            |
| Braun Menendez,<br>Case 1                | M   | 56  | 206            | 40               | Myocarditis. Syphilis  | Flutter Leads II and III.<br>Bundle-branch block                      | Syphilis at 27. Dyspnea since 45.  |
| 1934—Case 2                              | F   | 60  | 250            | 29               | B.P. 188/132; systolic<br>at apex                              | Flutter Leads II and III.<br>Left axis deviation                      | One yr. syncope and dyspnea; no<br>carotid sinus effect.   |
| Bizzozero, 1935                          | F   | 39  | 240            | 30               | Rheumatic mitral   | Flutter Leads II and III  | Atropine sulfate produced flutter in<br>complete heart-block; amyl nitrite<br>no effect.                                 |
| Van Dooren, 1935                         | M   | 58  | 330            | 43               | B.P. 190/60; nortitis;<br>systolic at base                     | Lead II shown   | Quinidine restored sinus auricular<br>control. Block persisted with<br>syncope.  |
| Soulie, Gatham,<br>and Bachmann,<br>1936 | F   | 66  | 200<br>280     | 30               | B.P. 280/150; arterio-<br>sclerotic                            | Left axis deviation   | After atropine developed slow flutter<br>but had had paroxysms of slow<br>flutter.                                       |
| Rouhier, 1936<br>Case 1                  | M   | 66  | 360            | 30               | B.P. 260/100; arterio-<br>sclerotic                            | Flutter Leads II and III.<br>Delay QRS                                | Syncope and slow pulse two yr.<br>Flutter eight mo. return sinus<br>auricular control.                                   |
| Case 2                                   | M   | 52  | 190            | 36               | B.P. 170/90; myocarditis                                       | Flutter Leads II and III.<br>Left axis deviation                      | Angina on effort for eight mo.   |
| Authors' case                            | M   | 67  | 270            | 30               | B.P. 178/62; arterio-<br>sclerotic; cardiac in-<br>sufficiency | Flutter Leads II and III.<br>Left axis deviation                      | Restoration of sinus auricular con-<br>trol with quinidine, temporary first<br>stage block, later complete A-V<br>block. |

## CASE REPORT

Italian, male, aged sixty-six years, formerly a restaurateur, complained of shortness of breath and weakness of two months' duration; a physician had advised him that he had "heart trouble." There was no history of previous illness. Two years previous he saw a doctor because of a "cold" and was told that his liver was enlarged. Nothing was said about his pulse and no medication was given.

Two months before admission, he had undergone considerable nervous strain and at that time he first noted a slow pulse. He suffered from progressive shortness of breath, palpitation, and dizziness. Because of these symptoms he was forced to sell his business one month before we saw him. More recently there had occurred some swelling of the ankles, loss of appetite, and epigastric discomfort after eating starchy food. He had lost twenty pounds by dieting during the past year. Otherwise the history was negative.

*Physical Examination.*—Revealed a rather obese male (25 lb. overweight for height and age); weight 190 lb.; height 5 ft. 8 in.; with evident respiratory distress; skin showed a slightly yellowish tinge; the mucous membranes were slightly cyanotic; eyes were negative except for subicteric sclerae; the pulse was 36, and

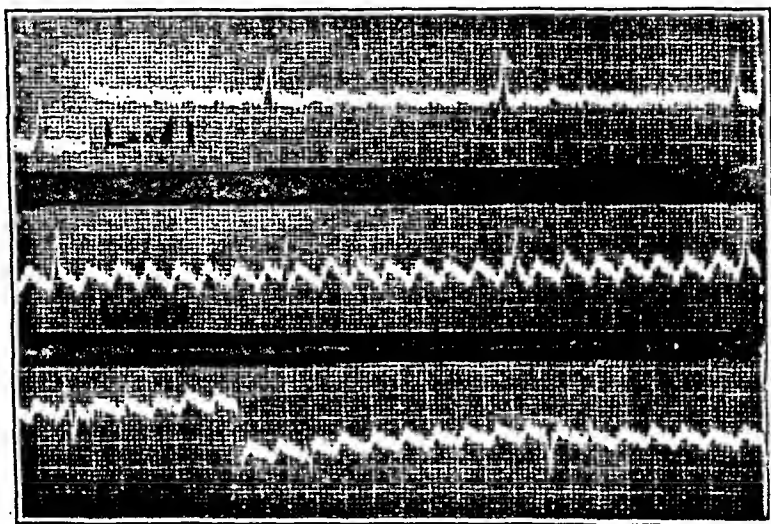


Fig. 1.—Auricular flutter, rate 270; complete heart-block; ventricular rate 36; tracing made before any treatment was given.

regular; the blood pressure was 178/62; there was slight distention of the jugular veins but no abnormal pulsation was observed; examination of the heart revealed diffuse enlargement which showed by the orthodiagram an M.R. of 7.5 cm. and an M.L. of 11 cm.; the heart tones were distant and muffled, with a systolic and a diastolic murmur at the apex, aortic area, and in the third interspace to the left of the sternum; the lungs showed emphysema but there were no signs of congestion or of fluid in the pleural spaces; the abdomen was negative except for the liver which was five cm. below the costal margin but not tender or pulsating; there was slight edema of the ankles.

*Laboratory Tests.*—Hemoglobin, 95 per cent; erythrocytes, 4,800,000; leucocytes, 4,200; with a differential count of: neutrophils, 45 per cent; lymphocytes, 48 per cent; eosinophils, 3 per cent; and myelocytes, 2 per cent. Urine: specific gravity 1.020; protein graded three plus to a slight trace in several specimens; a few hyaline casts and 30 leucocytes to the high-power field. Wassermann reaction: negative.

The fluoroscopic examination revealed slowly beating ventricles and a moderate globular enlargement of the heart; flutter of the auricles was not visualized. The electrocardiogram at this time demonstrated an auricular flutter with an auricular rate of 270 and a complete A-V dissociation with a ventricular rate of 36 (Fig. 1).

*Clinical Course.*—The patient was hospitalized and his progress followed with daily electrocardiograms. During hospitalization the weight dropped to 171 lb., a loss of 19 lb. Salyrgan 1 c.c. by intramuscular injection was used on two occasions. Digitalis,  $7\frac{1}{2}$  grains total, was given on the second and third day in the hospital. The digitalis was then discontinued and on the fifth day, quinidine sulfate was administered. Quinidine sulfate was given to tolerance on several occasions; October 16, the fifth hospital day, he received 31 grains of quinidine sulfate, and on the following day, 36 grains, when he developed nausea and gastric distress; at this time the pulse rose to 40 and an electrocardiogram showed a persistent flutter with an auricular rate of 130 (Fig. 2A). On the next day, October 18, quinidine sulfate, grains 18, was given when the patient again developed gastric distress and headache; the pulse rose to 58 on this day. The following day, October 19, quinidine sulfate, grains 24, was given; the pulse increased to 52 and an electrocardiogram showed a restoration of sinus rhythm with a first stage heart-block, the P-R interval being 0.72 seconds (Fig. 2B). Quinidine was continued for two more days in small doses and then withdrawn. In all, 109 grains of quinidine sulfate were given in four days, and 127 in six days. Electrocardiograms at various intervals for nearly seven

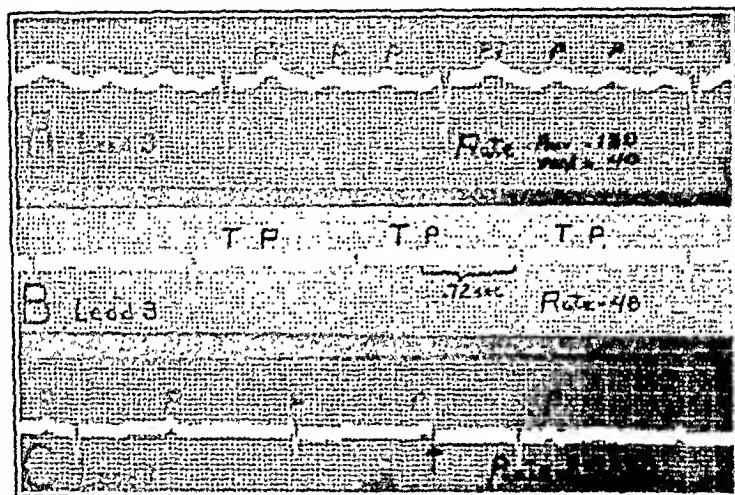


Fig. 2.—Showing response to quinidine. A, slow flutter after 67 grains of quinidine in two days; B, restoration of sinus rhythm with first stage heart-block after 109 grains of quinidine in four days; C, complete A-V dissociation which persisted after quinidine was discontinued.

months since that time, show a return of complete A-V dissociation with an auricular rate of 62 to 68 and a ventricular rate of 32 to 36 (Fig. 2C). Under the influence of quinidine there was a constant increase in pulse rate—on one occasion to 60 per minute. When the drug was withdrawn the pulse beat returned to the original rate, 36 to 38 (Fig. 2C). The blood pressure dropped during quinidine administration from 190/60 to 130/55, but after discontinuing the drug it rose to 166/60, at which level it has remained up to the present time.

#### COMMENT

This case of complete auriculoventricular block and auricular flutter developed several interesting changes on quinidine therapy. These were:

- (1) Slowing of auricular flutter rate. (2) Increase in ventricular rate. (3) Restoration of sinus rhythm, with first stage block. (4) Return of complete A-V dissociation with normal auricular rate.

1. *Reduction of the auricular flutter rate* from 270 (Fig. 1) to 130 (Fig. 2A) was observed as an effect of quinidine, which is known to depress the conductivity of the auricles, ventricles, and bundle of His, and to lengthen the refractory period of the muscle. Levine<sup>30</sup> states that quinidine therapy may reduce the auricular rate while the flutter still persists, as was noted in this case (Fig. 2A). De Boer<sup>28</sup> explains the abolition of the circus movement by quinidine as a result of depression of conductivity, lowering rate of impulse formation, and lengthening of refractory period. He believes that an increase in the refractory period at first establishes the circus movement more firmly, but when the muscle is made more refractory by quinidine, the circus movement may then be blocked. This reasoning may apply in the present case as an explanation for the reduction in the auricular rate to 130 by quinidine (Fig. 2A), even though the flutter persisted, as well as the subsequent establishment of sinus rhythm with an auricular rate of 48 (Fig. 2B).

2. *Increase in ventricular rate* frequently results from quinidine administration. Levine<sup>30</sup> and White<sup>29</sup> observed that the ventricular rate may be either slower or accelerated by quinidine. White believes that when the rate of the auricular circus movement diminishes, the A-V conduction improves. This assumes the presence of a physiological block only, which usually pertains to auricular flutter. The improvement in A-V conduction occurs despite the fact that quinidine depresses the conductivity of impulses through the bundle of His. The increased ventricular rate was manifest on several occasions when the quinidine was given to the point of intoxication. An electrocardiogram was obtained on one occasion when the ventricular rate was 48 (although at one time the pulse increased to 60). Electrocardiographic tracing revealed a sinus rhythm with a first stage heart-block (Fig. 2B).

3. *Restoration of sinus rhythm with first stage block*: in our patient was observed on only one occasion (Fig. 2B) and has been referred to in the previous paragraph. Complete auriculoventricular block recurred when the quinidine was discontinued (Fig. 2C). A persistent restoration of sinus rhythm was found by Schott,<sup>4</sup> Gallemaerts,<sup>9</sup> and Gager.<sup>17</sup> A first stage heart-block with a P-R interval of 0.24 second was reported by Gager;<sup>17</sup> the P-R interval shown in our tracings was 0.72 second (Fig. 2B); this is exceedingly long though Herrmann and Ashman<sup>16</sup> note one case with a P-R interval of 1.01 seconds. We feel that the restoration of sinus mechanism which occurred temporarily was due to marked slowing of the auricular rate to 48, which permitted impulses from the auricles to pass through the A-V node. This may be construed as evidence that there are conducting fibers present which are capable of transmitting impulses at a slow rate; however, when the auricular impulses reach the A-V node in rapid succession the node is not capable of accepting and transmitting them; it becomes refractory.

Thus when the auricular rate is that of flutter or even a normal rate of 70, the A-V dissociation is complete. We may, therefore, conclude that a physiological as well as an organic heart-block is present.

4. *Return of complete heart-block with normal auricular rate* occurred upon withdrawal of the quinidine sulfate and the subsequent return of the auricular rate to 70 (Fig. 2C). This conduction mechanism defect has remained constant during a period of six months' observation, in which the ventricular rate is found to persist at 36 to 38, and the auricular rate at 68 to 70. Since there have been no syncopal attacks, no real effort has been made to increase the ventricular rate or to employ any medication designed to decrease the block. We have hesitated to use large doses of atropine inasmuch as the patients reported by Jolly and Ritchie,<sup>1</sup> Soulie,<sup>25</sup> and Bizzozero,<sup>23</sup> developed auricular flutter after atropine was given. These patients previously had complete heart-block with sinus auricular control. However, on one occasion a small dose of atropine sulfate, grain  $\frac{1}{75}$ , was given. Curiously at this time an

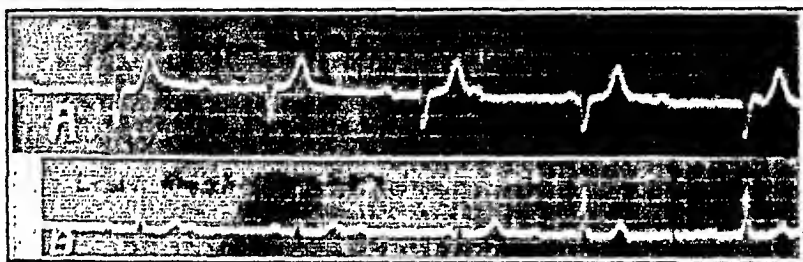


Fig. 3.—Showing the effect of  $\frac{1}{75}$  grain of atropine sulfate on ectopic ventricular focus A, before the injection of atropine; B, thirty minutes after injection.

electrocardiogram taken before administration of the drug indicated that the ventricles had assumed an ectopic focus (Fig. 3B). This degree of control by an ectopic focus has not been noted in several tracings made over a subsequent period of seven months. Thus the restoration of A-V rhythm control after atropine may have been coincidental. Levine states that atropine abolishes ectopic beats by increasing the heart rate through removal of the vagus effect. We observed no increase in ventricular rate despite the partial abolition of the ectopic focus.

#### SUMMARY

A case of spontaneous, complete auriculoventricular block associated with auricular flutter is reported. Treatment with quinidine reduced the auricular rate one-half and later resulted in restoration of the normal auricular rate with transient first stage heart-block and subsequent return to persistent, complete auriculoventricular block. Electrocardiograms after treatment with quinidine are shown and discussed. This combination of cardiac irregularities is rare and especially so

when, under treatment with quinidine, it goes through the stages of slow flutter, slow sinus rhythm with first stage heart-block and finally, return of complete heart-block.

# REFERENCES

1. Jolly, N. A., and Ritchie, N. T.: Auricular Flutter and Fibrillation, *Heart* 2: 177, 1910-11.
2. Hertz, A. F., and Goodhart, G. W.: The Speed of the Human Heart, *Quart. J. Med.* 2: 213, 1909.
3. Donzelot, E., and Pezzi, C.: Tachysystole de l'oreillette avec dissociation atrio-ventriculaire complete, *Bull. et mém. Soc. méd. d. hôp de Paris* 37: 497, 1914.
4. Schott, E.: Über Ventrikelstillstand (Adams-Stokes'sche Anfalle) nebst Bemerkungen über andersartige arhythmien passagerer natur, *Deutsches Arch. f. klin. Med.* 131: 211, 1920.
5. Vinnis, E. W. G.: Disharmonie tusschen atrium en Ventrikel. Rythm in zyn Sterkalen Vorm., *Nederl. maandschr. v. geneesk.* 9: 117, 1920.
6. Arrillaga, F. C., and Waldorf, C. P.: La taquisistolia auricular enei sindrom de Morgagni, Stokes-Adams, *Rev. Asoc. méd. argent.* 34: 96, 1921.
7. Keating, J. H., and Hajek, J.: Auricular Flutter, *Am. J. M. Sc.* 164: 656, 1922.
8. Wiltshire, H.: Heart Block Illustrating Behavior of the Auricle During Periods of Prolonged Ventricular Silences, *Heart* 10: 201, 1923.
9. Gallemaerts, V.: Tachysystolie auriculaire et bradycardie (Soc. clin. Hop. Bruxelles, 1923), *Arch. d. mal. du coeur* 17: 529, abstract, 1924.
10. Hall, V.: Auriculo-Ventricular Bundle-Branch Block, *Brit. M. J.* 1: 778, 1924.
11. Willius, F. A.: Auricular Flutter With Established Complete Heart-Block, *AM. HEART J.* 2: 449, 1927.
12. Strauss, A. E.: Heart-Block, Auricular Flutter and Adenoma of the Thyroid, *M. Clin. North America* 11: 487, 1927.
13. Parkinson, J., and Bedford, D. E.: Course and Treatment of Auricular Flutter, *Quart. J. Med.* 21: 21, 1927.
14. Henderson, J., and Rennie, J. K.: Case of Auricular Flutter With Full Heart Block, *Glasgow M. J.* 58: 355, 1927.
15. Lian, C., and Viau, C.: Auricular flutter et bradycardie par dissociation auriculo-ventriculaire complete, *Arch. d. mal. du coeur* 23: 514, 1930.
16. Herrmann, G., and Ashman, R.: Partial Bundle-Branch Block; Theoretical Consideration of Transient Normal Introventricular Conduction in Presence of Apparently Complete Bundle-Branch Block, *AM. HEART J.* 6: 375, 1931.
17. Gager, L. T.: Auricular Flutter and Complete Heart Block With Restoration of Sinus Rhythm and A-V Conduction, *Ann. Int. Med.* 5: 463, 1931.
18. Bosco, J. J., and Vega, M. N.: Auricular Flutter With Complete A-V Dissociation, *Rev. med. latino-am.* 16 n°: 188, 1931.
19. Braun Menendez, E.: Auricular Flutter and Complete A-V Block, *Ann. Int. Munic Rad. y Tisiother.* 1: 309, 1934.
20. Parsonnet, J., and Parent, S.: Auricular Flutter With Complete Auriculo-Ventricular Block in a Patient With Coronary Disease, *Arch. Int. Med.* 51: 938, 1933.
21. Martinez, G. N.: A Syndrome of Heart-Block With Auricular Flutter With the Probable Etiology, 1° Congr. Nacion Med., Buenos Ayres 2: 321, 1916.
22. Ramos, J.: Complete A-V Block Associated With Auricular Flutter With Lesion of Two Branches of Bundle of His, *Rev. biol. e hyg.* 3: 68, 1932.
23. Bizzozero, R. C.: Bloqueo auriculo-ventriculaire asociado a un aleteo auricular, *Arch. cardiol. y hemat.* 16: 33, 1935.
24. Van Dooren, M. F.: A Case of Complete A-V Block With Auricular Flutter, *Soc. Cli. Hop. Bruxelles* 3: 128, 1935.
25. Soulie, P., and Cattani, R.: A-V Dissociation With Paroxysmal Auricular Flutter, *Bull. et mém. Soc. Méd. d. hôp. de Paris* 52: 445, 1936.
26. Routier, D., Mamon, Henry, and Le Mant, J.: Complete Heart-Block and Auricular Flutter, *Arch. d. mal. du coeur* 29: 369, 1936.
27. Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Relation to Heart-Block, *AM. HEART J.* 29: 4, 559, 1928.
28. De Boer, S.: Auricular Flutter and Auricular Fibrillation in Total Heart-Block, *Nederl. tijdschr. v. geneesk.* 1: 550, 1924.
29. White, Paul Dudley: Heart Disease, 1931, The Macmillan Company.
30. Levine, S. A.: Clinical Heart Disease, 1936, W. B. Saunders Company.



## Department of Clinical Reports

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### A CASE OF TRICUSPID STENOSIS WITH ENORMOUS DILATATION OF THE RIGHT AURICLE\*

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TRICUSPID stenosis can no longer be considered a very rare condition. About 250 cases have been reported in the literature<sup>1</sup> and it seems probable that there have been other cases diagnosed during life or at post-mortem examination which have not been reported.

There have been two cases at Barnes Hospital with a diagnosis of tricuspid stenosis established by autopsy findings from a total of 2,728 autopsies during the years 1914 to 1937. One was the case of a forty-one-year-old white woman with the usual symptoms of dyspnea, orthopnea, dependent edema, ascites, and cyanosis for about one year before death. There was a history of rheumatic fever when she was twenty-nine years old. At autopsy there was dilatation of all the chambers of the heart. The mitral and tricuspid orifices were each so narrowed that only the tip of the little finger could be admitted.

The other patient presented such unusual findings that it is considered worthwhile to report it in some detail.

#### CASE REPORT

C. A. S., a forty-three-year-old white woman, was admitted to Barnes Hospital four times and was observed over a period of more than two years. Her past history revealed neither major nor minor manifestations of rheumatic fever. She had a congenital kyphosis and scoliosis of an extreme degree. An attack of typhoid fever at the age of thirty-one years had been followed by an uneventful recovery. She married at the age of twenty and had two healthy children. During her first pregnancy a right-sided femoral hernia developed. A contralateral femoral hernia appeared during the second pregnancy four years later.

Symptoms of circulatory difficulty were first noted at the age of thirty-one following an operation for repair of the bilateral hernia. She recovered with difficulty from the anesthetic, and for the next two years suffered from frequent attacks of fainting. These finally disappeared, but after three years of apparent good health she noticed a gradually increasing swelling of her ankles and dyspnea on exertion. She was found to be pregnant and was aborted at seven months. Following this episode her face, legs, and abdomen started to swell, and other signs of cardiac failure made their appearance. Green pills were administered on several occasions by her physician, and once an abdominal paracentesis was performed which yielded

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two gallons of greenish fluid. Dyspnea, edema, and palpitation continued; later, orthopnea, cyanosis, and expectoration of bloody sputum were noted, and the patient entered Barnes Hospital in January, 1934, for treatment.

Physical examination revealed an undernourished woman sitting up in bed and severely dyspneic. She was intensely cyanotic. Her spine was deformed by an extreme degree of kyphosis and scoliosis, and the lower portion of the sternum was depressed. The superficial veins of the chest and abdomen were distended. The jugular veins were greatly distended, but did not pulsate. Both lung bases were dull to percussion and were filled with moist râles. The heart dullness extended to



Fig. 1.—Postero-anterior roentgenogram of the chest showing the extreme degree of right- and left-sided enlargement of the heart.

the axillary line in the fifth intercostal space on either side. Systolic and diastolic murmurs were heard over the entire precordium, loudest at the mitral area, and a diastolic thrill could be felt over the precordium and toward the left axilla. The second pulmonic sound was soft and faint. The auricles were in fibrillation. The blood pressure was 130/70. The liver was nodular, extended to the umbilicus, and did not pulsate. There was no ascites or pitting edema of the lower extremities. A large reducible femoral hernia was present on the left.

Shortly after admission the hernia became incarcerated and an immediate operation was performed. She almost expired during the course of the operation, but the subsequent post-operative course was uneventful. Following digitalization there was

considerable improvement in her condition, and she was discharged, to be followed in the heart clinic. Improvement, however, was only temporary, and during the next two years her symptoms became progressively worse. Persistent ascites was controlled to some extent by salyrgan. During this period she entered Barnes Hospital three times for symptomatic treatment. On one occasion one observer believed that the liver could be felt to pulsate, but this was not confirmed, and in general there was no change in the physical signs. She was admitted for the last time in February, 1936. Respiratory embarrassment was extreme, but the chest findings were essentially as before. The abdomen was greatly distended with fluid, and no organs could be felt. The patient was in such great distress that it was felt advisable to perform

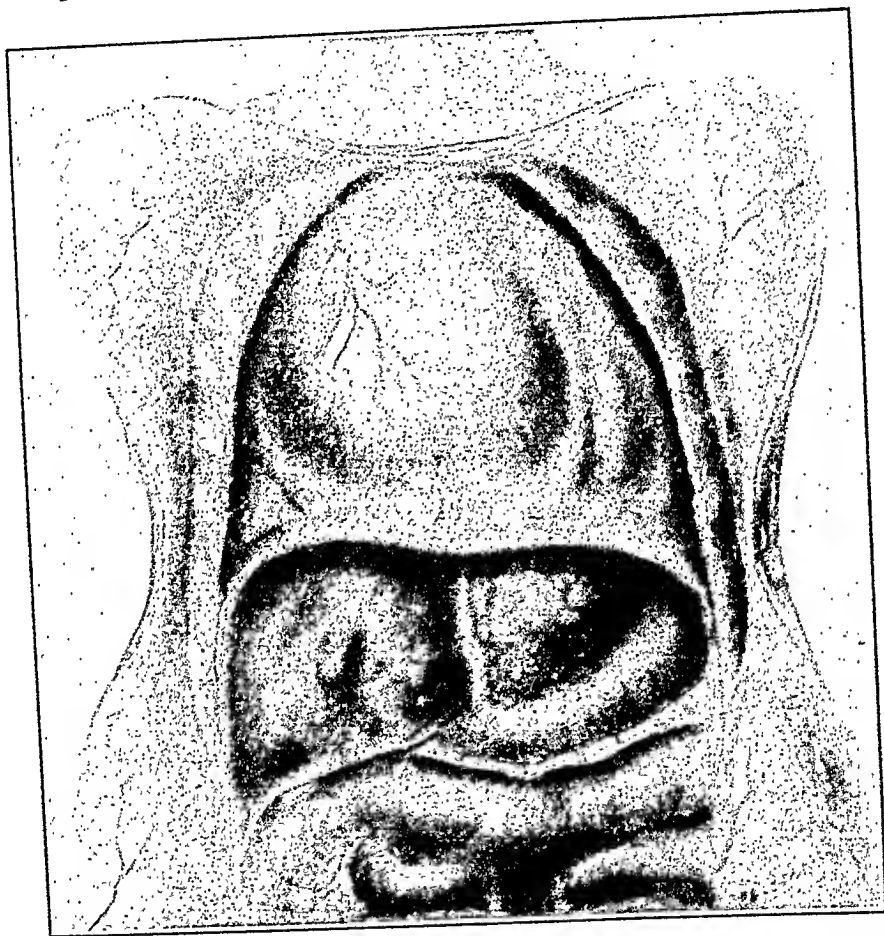


Fig. 2.—Drawing of the thoracic and abdominal cavities with the organs exposed in situ. The lungs are posterior to the heart.

a paracentesis. Fifty-five hundred cubic centimeters of very dark bloody fluid were withdrawn from the abdomen. The patient expired shortly afterward.

During the period when the patient was under observation the laboratory and fluoroscopic findings changed but little. There was a moderate anemia (red blood corpuscles numbered 3,500,000 with hemoglobin 67 per cent); the urine was negative and the blood Kahn was negative. The blood nonprotein nitrogen, calcium, and phosphorus were within normal limits. Electrocardiograms showed auricular fibrillation, slurring of the QRS complexes, right axis deviation, and a negative Dieuaide's sign. Roentgen ray films of the chest showed a heart shadow extending almost to the lateral chest wall on either side and increased lung markings. On fluoroscopy the right side of the heart could not be seen to pulsate; there was a clear posterior

mediastinal space. Venous pressures by direct measurement were 12 cm. and 20 cm. of water on two occasions. The velocity of blood flow, as determined by the decholin method, was 20 seconds and 28 seconds on two occasions. Because of the possibility that there was a massive pericardial effusion a needle was introduced 2 cm. anterior to the right mid-axillary line and 1 cm. into the thorax, and pure blood was withdrawn. Oxygen content determinations showed this to be venous, and established the fact that the needle had entered the right auricle.

*Relevant post-mortem findings.*—Post-mortem examination disclosed an emaciated middle-aged woman with pitting edema and reddish-brown discoloration of the lower extremities. There was an extreme scoliosis of the thoracic spine to the right. Two liters of blood-tinged fluid were found in the peritoneal cavity. All the vessels of the peritoneum were engorged. The pleural cavity contained no excess fluid and no

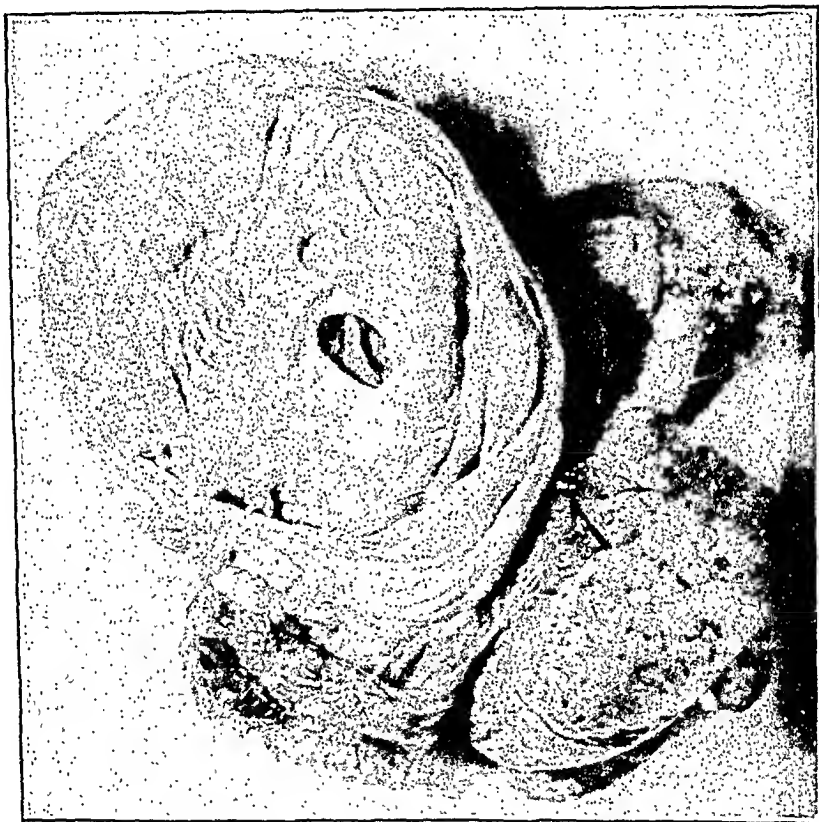


Fig. 3.—The endocardial surface of the right auricle with the stenotic tricuspid orifice.

adhesions. The pathological diagnoses were: (1) chronic rheumatic (?) endocarditis of the mitral and tricuspid valves with insufficiency and stenosis; (2) adherent pericardium over the right auricle only; (3) enormous dilatation of the right auricle; (4) scarring and hypertrophy of the muscle fibers of the right auricle; (5) slight dilatation and hypertrophy of the right ventricle; (6) partial pulmonary atelectasis (compression); (7) ascites and edema of the ankles; (8) congestion of the liver, spleen, and peritoneal tissues; (9) marked scarring of the liver; (10) scoliosis of the thoracic vertebrae; (11) slight aortic atherosclerosis.

*Heart:* The heart and pericardial sac occupied most of the chest cavity and completely hid the lungs from view. The pericardial sac was found to be adherent over the right auricle with the exception of the appendage and an area adjacent to it. There were no mediastinal or pleural adhesions, nor was the pericardium adherent over the other chambers of the heart. On removing the heart from the chest cavity the major part of it was seen to be right auricle. Its wall was about two-thirds its normal thickness, but it must have had a great increase in substance since

it was not strikingly thin in spite of its great size. There were smooth white plaques in the endocardium lining the auricular appendage which were probably old organized thrombi. The endocardium was somewhat thickened and opaque toward the edge of the tricuspid ring. The capacity of the right auricle was 2,150 c.c. The right ventricle was only a little larger than normal, and its wall was of about normal thickness. It had a capacity of about 100 c.c. The left auricle was neither dilated nor hypertrophied; its contents measured 95 to 100 c.c. The endocardium above the mitral valve was opaque, but there was no definite auricular patch of rheumatism. The left ventricle was of normal size. The tricuspid cusps were fused, forming a rounded opening with moderately thick and retracted edges which measured 7 cm. in circumference and were incapable of closing. The chordae tendinae were thickened. The mitral valve was thickened and retracted so that the division into cusps was no longer apparent. Its circumference was 5 cm. The circumferences of the

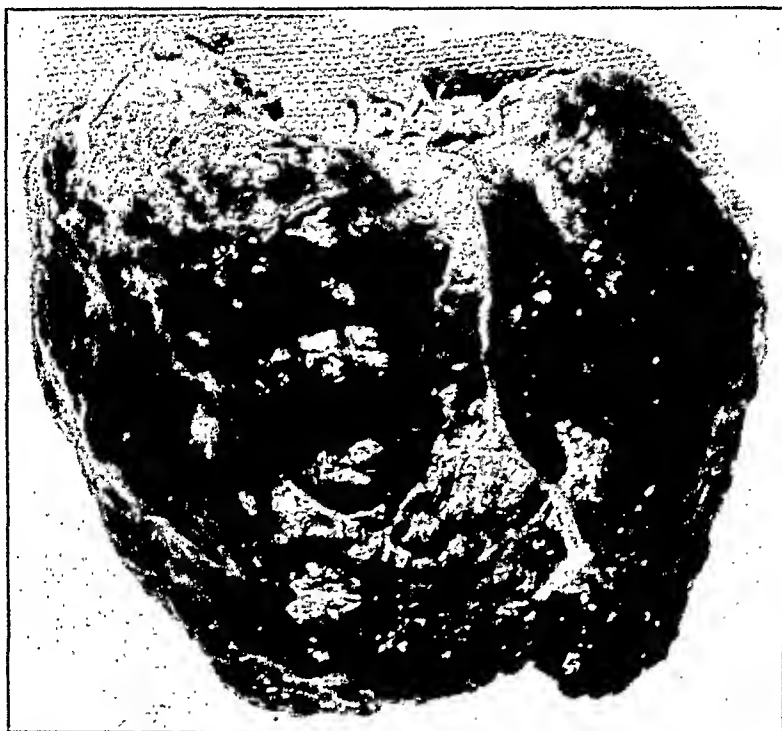


Fig. 4.—The small, atrophic liver with its irregularly nodular surface.

pulmonary and aortic valves were 10 cm. and 7.75 cm. respectively. They were normal in appearance. The heart weighed only 595 gm. in spite of the tremendous right auricle.

On microscopic examination the bundles of muscle fibers of the right auricle were greatly hypertrophied and were interspersed with vascular and cellular connective tissue. In some places there were only thin strands of interrupted hypertrophied fibers. The nuclei of the muscle fibers were large and hyperchromatic. There was a moderate hypertrophy of the muscle fibers of the right ventricle and left auricle and none of the left ventricle. No Aschoff bodies were seen.

*Lungs:* The lungs were compressed and lay posteriorly to the heart. There was a partial collapse of the lower lobes, especially of the left. They showed a surprisingly small amount of congestion. On section there were seen alternating areas of collapse and overdilatation of the alveoli. Some of the partially collapsed areas showed a little blood in the alveoli. The pulmonary artery showed no intimal changes.

*Liver:* The liver was smaller than normal, weighing 1,285 gm. The surface was irregularly nodular, and variation in the size of the nodules was greater than is usual in cirrhosis. The capsule was somewhat thickened, and the cut surface was of a deep red color and firmer than normal, as if containing an excess of connective tissue. Although there were some areas which were more congested than others, they did not seem to correspond to the normal central portions of the lobules, but were larger and less regular in arrangement. Little normal lobulation was seen. On section lobules with normal relations to central veins were distinguishable. In these areas the periportal tissue contained scarcely more connective tissue than usual and a few wandering cells. The sinuses about the central veins were widened and the liver cells atrophied. Other zones, however, showed wide communicating bands of connective tissue containing small bile ducts, a few lymphocytes and plasma cells, and occasional hemorrhages. Many such zones connected with the thickened capsule.

*Spine:* There was a marked curvature to the right which extended from the fourth to the tenth thoracic vertebra, and there was a maximum deviation of 6.5 cm. from the midline. Microscopic section offered no clue as to the etiology of the curvature.

#### DISCUSSION

The diagnosis of tricuspid stenosis was not made in this case before death. It was recognized, however, that the patient had an enormously distended right auricle, together with a left auricle which was little or not at all dilated. The aspiration of venous blood from the right chest and the persistently clear posterior mediastinal space established this. Therefore, only those conditions which might lead to isolated hypertrophy of the right side of the heart were considered. Although Broadbent's sign and diaphragmatic tug were absent, the question of mediastinopericarditis was raised on the basis of fixation of the cardiac shadow, a negative Dieulaide's sign, the presence of periapical recession about the apex, and persistence of ascites after disappearance of edema of the lower extremities following digitalization. A patent foramen ovale in the presence of mitral stenosis was considered in view of the enormous size of the right auricle and the presence of another congenital defect, viz., the curvature of the spine. Against this was the soft quality of the pulmonic second sound and the long-standing cyanosis. Although tricuspid stenosis was considered, the failure to identify a diastolic thrill and murmur localized at the tricuspid area or other strictly characteristic signs prohibited a definite diagnosis.

Tricuspid stenosis may be either a congenital defect or the result of rheumatic heart disease. In the majority of cases, however, it is due to the latter<sup>2</sup> even in the absence of a history of frank rheumatic heart disease. Often enough one can elicit a history of "minor rheumatic manifestations" described by Kaiser.<sup>3</sup> In the case reported above there is considerable room for speculation in regard to the cause of the heart lesions. The absence of a history of rheumatic manifestations of any sort; the presence of a congenital spinal deformity, a condition occasionally associated with congenital heart lesions; and the smooth and rounded appearance of the tricuspid valve instead of the irregular

ciatrization characteristic of endocarditis<sup>1</sup> are in favor of the congenital origin of the condition. On the other hand, the absence of a deficient auricular septum (an almost inevitable consequence of congenital right heart valvular obstruction<sup>4</sup>) and the appearance of cyanosis in adult life rather than in infancy offer almost unequivocal evidence that the cardiac defects were acquired.

The possibility that the spinal deformity acted as a contributing cause of the changes in the heart is difficult to evaluate. In cases of extreme kyphoscoliosis there is often diminution of the pulmonary blood stream and compression of the great vessels. As a result of this considerable strain is thrown on the ventricles, which become secondarily hypertrophied and dilated.<sup>5</sup> In view of the fact that in this case the changes in the ventricular myocardium were comparatively insignificant, one may conclude that the effects of the chest deformity on the heart were minimal.

Patients with tricuspid stenosis not uncommonly live for many years after the appearance of evidences of congestive failure,<sup>6</sup> a fact well exemplified by this patient who suffered for ten years with an almost continual state of cardiac decompensation. In spite of an extreme mitral stenosis the left auricle was of normal size, and one must believe that the left heart was spared at the expense of the right and that the right auricle acted as a reservoir from which blood was not admitted to the right ventricle and left heart with sufficient rapidity to cause hypertrophy or dilatation. For this reason the pressure in the pulmonary vessels was low, the second pulmonic sound was soft and faint, and pulmonary congestion was not a prominent feature. The increased pressure was apparent chiefly in the peripheral venous circulation and symptoms of extreme edema and ascites were prominent throughout the course of the disease. The circulation was slowed sufficiently to result in intense cyanosis. Thus, patients with this condition have a longer life expectancy than those with uncomplicated mitral stenosis because the heart is relieved of the strain at the expense of the peripheral vascular system.

Tricuspid stenosis most frequently occurs in association with mitral stenosis.<sup>7</sup> A study of the reported cases in which these two lesions were associated reveals a striking diversity in the state of the heart chambers in the presence of a certain uniformity of the valvular lesions. For example, in most cases there is some dilatation of the right auricle, but often all the chambers show dilatation and hypertrophy. Sometimes the left side of the heart is more greatly affected than the right, sometimes the right more than the left. Rarely the right auricle alone is dilated<sup>2</sup> (case 1), or the size of the chambers is essentially normal.<sup>1</sup> Griffith<sup>8</sup> has pointed out that isolated stenosis of the tricuspid valve is extremely rare, and remarks that in view of the fact that mitral stenosis often occurs alone one is led to the inference that tricuspid stenosis



is secondary to mitral stenosis. It seems logical to conclude, therefore, that the effect of the stenoses on the heart as a whole depends not only on the degree of stenosis, but especially on the time interval that elapses between the mitral and tricuspid affections. Thus, for example, when the left auricle is greatly dilated, it might be inferred that the mitral valve was narrowed for a considerable period of time before the tricuspid. On the other hand, when the right auricle is especially dilated, it can only mean that the left side of the heart has been spared by the tricuspid lesion and that the mitral lesion antedated the tricuspid by only a short interval of time.

In the case reported above it seems likely that tricuspid stenosis appeared early in the course of the endocarditic process with a consequent result of a huge dilatation of the right auricle together with approximately normal-sized left auricle and ventricle. The great enlargement of the right auricle was undoubtedly enhanced by the long-standing fibrillation. The strain of the venous column of blood was thrown entirely on the passive walls of the right auricle which were unable to contribute to the forcing of the blood through the auriculoventricular opening.

The liver presented a complex and somewhat confused picture. Grossly it showed the typical picture of the so-called "nutmeg liver" resulting from long-continued stasis with collapse and fibrosis. Microscopic examination revealed a striking degree of degeneration and connective tissue infiltration, which corresponded to the final stage of "collapse fibrosis" described by Lambert and Allison.<sup>9</sup> It is noteworthy that in spite of the protracted course of the disease and the advanced pathological alterations, the changes were not diffuse throughout the liver, but were much more prominent in some areas than in others. This variability has been noted by Lambert and Allison and other workers. However, in this case the connective tissue increase was not confined to the regions around the center of the lobules, but irregularly involved the portal spaces. Here and there the connective tissue of Glisson's capsule surrounded whole groups of lobules. Such a picture has been described as occasionally occurring in the "cardiac liver,"<sup>10</sup> but it is apparently not characteristic of this condition, and leaves some room for doubt whether all the changes can be ascribed to chronic passive congestion, or whether, as has been observed in rare cases, some of the changes were the result of a true portal cirrhosis.

#### SUMMARY

A case of mitral and tricuspid stenosis has been described. Remarkable was the huge dilatation of the right auricle while the other chambers of the heart were of approximately normal size. The probable cause of this isolated dilatation has been discussed. Remarkable, too, was the advanced collapse and fibrosis of the liver, which may have been



due entirely to long-continued chronic passive congestion or possibly to a combination of stasis and a true portal cirrhosis.

## REFERENCES

1. Clements, A. B.: Isolated Tricuspid Stenosis of Probable Rheumatic Origin, *Am. J. M. Sc.* 190: 389, 1935.
2. Fletcher, T. B.: Tricuspid Stenosis With a Report of Five Cases, *Am. J. M. Sc.* 142: 625, 1911.
3. Kaiser, A. D.: Factors That Influence Rheumatic Disease in Children, *J. A. M. A.* 103: 886, 1934.
4. Herrick, J. B.: Tricuspid Stenosis With Reports of Three Cases With Autopsies Together With Abstracts of 40 Cases Reported Since Lendet's Thesis (1888), *Boston M. & S. J.* 136: 245, 1897.
5. Edeiken, J.: The Effect of Spinal Deformities on the Heart, *Am. J. M. Sc.* 186: 99, 1933.
6. Zeisler: Tricuspid Stenosis, *AM. HEART J.* 8: 697, 1933.
7. Cottin, E., and Saloz, M. C.: A Case of Tricuspid Stenosis, *Arch. d. mal. du coeur* 13: 481, 1920.
8. Griffith, T. W.: On Affections of the Tricuspid Valve of the Heart, With a Note on a Pedunculated Thrombus Occurring in the Right Auricle, *Edinburgh M. J.* 13: 105, 1903.
9. Lambert, R. A., and Allison, B. R.: Types of Lesions in Chronic Passive Congestion of the Liver, *Bull. Johns Hopkins Hosp.* 27: 359, 1916.
10. Kaufmann, E.: *Pathology for Students and Practitioners*, Vol. II, Philadelphia, 1929, P. Blakiston's Sons and Co., p. 892.

## BUNDLE-BRANCH BLOCK IN A NORMAL YOUNG MAN

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EPINGER and Rothberger<sup>6</sup> were the first to demonstrate the characteristic electrocardiographic curves after section of a bundle-branch in dogs. Cohn and Lewis<sup>3</sup> showed the pathological changes in the hearts of four persons who during life had the characteristic curves; two of these hearts showed a lesion causing a disappearance of the bundle fibres: and of the other two one showed increased fibrous tissue in the ventricular septum, while the other had intact main stem and branches with obliteration of the smaller branches by connective tissue.

Bach<sup>1</sup> has subdivided the clinical cases into three groups according to their etiology, cardiovascular degeneration, syphilis, and rheumatism.

Von Deesten and Dolganos<sup>18</sup> add another group in which the curve is of an atypical variety and the prognosis is good.

More recently Wood and his associates<sup>22</sup> have published a follow-up of 64 similar cases.

Wolffe, Parkinson, and White<sup>21</sup> describe a fifth group occurring in healthy young people prone to paroxysmal tachycardia. They give reference to a case of Wedd's of a similar kind; Holzmann and Scherf<sup>10</sup> described two similar cases; while Pezzi<sup>15</sup> recorded three more under the heading "permanent paraseptal rhythm." Chen Lang Tung<sup>2</sup> described another similar case under the heading "functional bundle-branch block." Sigler<sup>17</sup> wrote of functional bundle-branch block paradoxically relieved by vagal stimulation.

It is probably to this fifth group that the case reported here belongs.

R. R., aged twenty-one years, apparently in perfect health, applied for employment. In the course of routine medical examination an electrocardiogram showed bundle-branch block of the uncommon variety (left bundle-branch block, old terminology) with a short P-R interval. Careful questioning on two occasions revealed a history of chickenpox at the age of three years and measles at the age of five years. There was no history of rheumatic fever, chorea, growing pains, scarlet fever, or venereal disease. There had never been any shortness of breath or symptoms to suggest paroxysmal tachycardia. He was a moderate smoker.

On examination he was well built and healthy looking. The heart was normal in size and shape clinically and radiologically. The heart sounds were normal. Blood pressure was 140/80, the arteries were soft. The pulse frequency varied between 80 and 90 per minute, sinus arrhythmia was present. The remainder of the clinical examination was negative. The effort test was very good, and blood Wassermann was negative.

The electrocardiogram showed the following time relationships:

P-T 0.5 second (Leads I, II, and III)  
P-Q 0.1 to 0.12 second  
P-S 0.24 to 0.28 second,

compared with the time relationships of a normal control

P-T 0.48 second  
 P-Q 0.18 second  
 P-S 0.22 to 0.24 second

compared with a typical case of bundle-branch block

P-T 0.52 second  
 P-Q 0.22 second (+ or -)  
 P-S 0.26 to 0.28 second.

Considering the divergent views on the intraventricular block in these cases, the following tests were carried out: (1) Effect of deep breathing, (2) Pressure on the vagi, first right then left, (3) Exercise, (4) One-fiftieth of a grain of sodium trinitrini by mouth, (5) One-hundredth of a grain of atropine subcutaneously.

No change in the shape of the curve was noted in the first four tests. Forty minutes after the injection of atropine there was a change in the

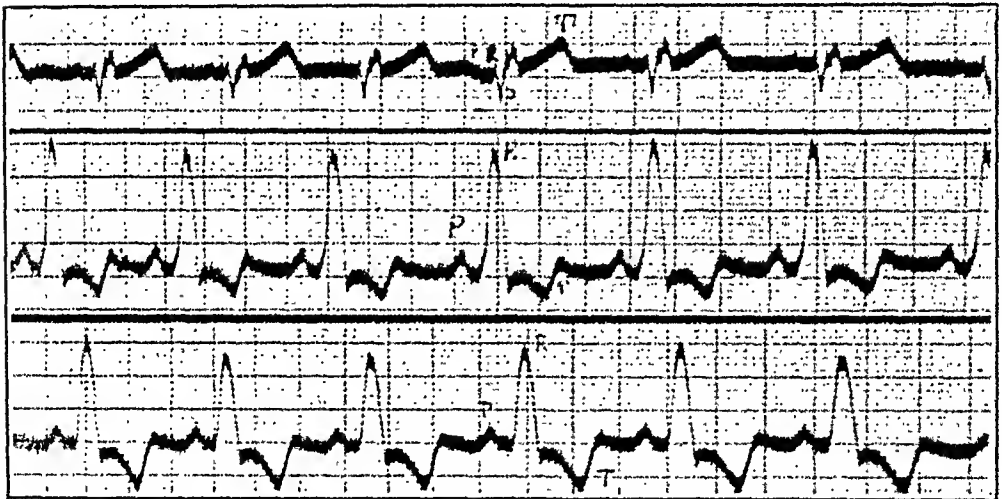


Fig. 1.—R. R., aged twenty-one years. Bundle-branch block; before atropine.

shape of the T-waves in Leads II and III, which became more marked in sixty minutes. Before giving atropine the T-wave was inverted in Lead II, with a slightly diphasic wave, and deeply inverted in Lead III; the atropine caused a more vertical T-wave in Lead II and a diphasic wave in Lead III; there was also a slight lengthening of the S-T period. There was no change in the P-R interval (which varied in different leads from 0.9 to 0.12 second) or of the QRS period which remained 0.12 second, the P-waves increased in amplitude.

It was not possible to repeat the experiment with larger doses of atropine as the young man went abroad.

#### DISCUSSION

*Prognosis.*—The significance of bundle-branch block is, according to King,<sup>13</sup> very grave regardless of etiology, though it appears best in those cases of rheumatic etiology. King showed that of 104 patients, 76 were

dead at an average of one year from the time of the discovery of the condition. He gives two years and eight months as the expectation of life in the rheumatic group.

Bach gives a slightly better prognosis for the cardiovascular degenerative group, describing cases of fourteen, nine, and seven years' duration. Graybiel and Sprague<sup>5</sup> record an average duration of one year and two months in 223 fatal cases out of 308 cases followed up.

Van Deesten and Dolganos in their atypical group (QRS prolonged, R in Lead I of moderate amplitude and short duration, S in Lead II prolonged and notched), show periods of eleven and one-half, eight, and two and one-half years, the patients being still alive. Wood and his associates gave similar findings.

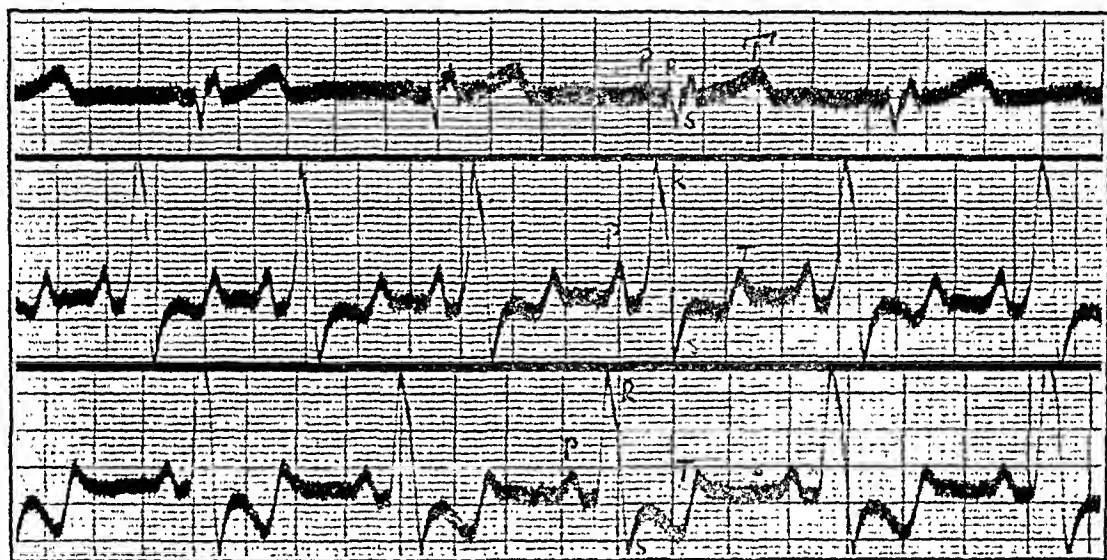


Fig. 2.—R. R., after atropine.

Wolffe, Parkinson, and White state of their particular group that there is no indication of heart disease, and record a case of fourteen years' observation, and no deaths in their series.

The case described here falls into the last group and has therefore a good prognosis as far as present knowledge can tell.

*Mechanism of the Bundle-Branch Block.*—Various views have been formulated on the mechanism of this form of bundle-branch block. There is no record of a post-mortem examination with careful histological research on a case of this kind.

Vagal tone has been considered to be the causative factor, and Wolffe, Parkinson, and White favor this view. They postulate a paradoxical vagal effect as the explanation of the shortened P-R interval, or in other words, release of vagal tone is accompanied by lengthening of the P-R interval. In their report of eleven cases they record that vagal compression in one case changed a normal type of curve to that of widened QRS and shortened P-R interval, while exercise in another case restored a normal curve which, with the person at rest, showed intra-

ventricular block. In two other cases intraventricular conduction was normal during attacks of paroxysmal tachycardia; there was no record of variation in the intraventricular conduction in four cases.

Wilson described a patient who, on taking a deep breath, changed a normal ventricular conduction into that characteristic of intraventricular block; the P-R interval also shortened from 0.17 second to 0.1 second.

Hering<sup>9</sup> recorded abnormal ventricular complexes during vagal stimulation in a dog, in which each abnormal ventricular complex was preceded by an auricular complex.

On the other hand Sigler<sup>17</sup> recorded a return to normal intraventricular conduction in two cases of bundle-branch block, one after thirty hops and the other after vagal compression. Also Gaskell<sup>7</sup> showed that the rate of conduction from auricle to ventricle may be depressed by vagal stimulation in animals, i.e., P-R interval increased; and Ritchie<sup>16</sup> found that compression of the vagus does not as a rule cause any depression of conductivity in the auriculoventricular bundle, although rarely compression of the right vagus may lengthen the auriculoventricular conduction time. No mention is made of decrease of auriculoventricular conduction time. Ritchie also found no change in the length of ventricular systole, with one exception when a ventricular beat lengthened from 0.35 second to 0.45 second.

Lewis and Master<sup>14</sup> found that 2:1 heart-block could be produced in the mammalian heart by vagal stimulation, but that the refractory period of the tissue concerned in auriculoventricular conduction is less influenced than that of auricular muscle by vagal stimulation.

Drury and Mackenzie<sup>4</sup> proved by their experiments that vagal stimulation in the dog has no influence on impulses spreading in the bundle branches or through ventricular muscle. They postulate that vagal stimulation may increase the gradient of decrement at higher levels (e.g., auriculoventricular bundle) or decrease the impulse strength at this higher level, then the impulse will be below normal strength when it arrives at the bundle branches. They state that a local condition constantly present and not connected with vagal stimulation may steepen the gradient more in one branch than the other so that the weakened impulse will be relatively more delayed in one branch than the other or even run to extinction.

In those conditions in which complete vagal heart block is present and the idioventricular beats are abnormal they feel that the more likely explanation is that impulses arise in the bundle above its bifurcation and are subject to decremental conduction rather than that they arise in a bundle branch.

Einthoven<sup>5</sup> described flattening and inversion of the T-waves in the dog during vagal compression, but no mention of change in the P-R or QRS intervals.

The experiment with atropine on the case described did not affect the P-R interval or the wide QRS wave, but did tend to elevate the T-waves. Vagus compression and exercise were without effect.

To sum up with regard to the vagal theory; Wolffe, Parkinson, and White, and Wilson and Hering, bring some experimental reasons in its favor, but it is difficult to correlate them with the generally accepted views of vagus function. Also in the case described apart from the change in the T-waves, after atropine injection, there was no evidence of vagal influence.

Pezzi believed that the abnormality of the ventricular complex was due to a paraseptal rhythm which would also explain the short P-R interval. The presence of ectopic ventricular beats in other cases, the vertical P-wave and the permanence as a rule of the condition, do not support his theory.

Holzmann and Scherf<sup>10</sup> postulate an abnormal path connecting the auricle and ventricle which misses the auricular and ventricular nodes. Wolferth and Wood<sup>20</sup> write that all the data so far obtained are in keeping with the possibility that an accessory pathway of auriculo-ventricular conduction (such as described by Kent between right auricle and right ventricle) could be responsible for the phenomena manifested by these cases. The anatomical evidence of this path is not, however, completely conclusive.

Measurements of P-T and P-S times in this tracing, in normal tracings, and in ordinary bundle-branch block tracings have been given for comparison as it has been suggested that there is no lengthening of the total P-T periods as in ordinary bundle-branch block.

It has been postulated that the QRS is prolonged as there is a premature contraction of one bundle due to the impulse passing down the bundle of Kent instead of in the auriculoventricular bundle with resulting shortening of the P-R interval.\*

It is difficult to believe any of the functional theories and not to feel that there is probably a mechanical abnormality in the bundle-branch system due to a local nonprogressive lesion. The fact that normal intra-ventricular conduction may sometimes occur temporarily is not a contra-indication to a lesion in the bundle. Hermann and Ashman described transient normal intraventricular conduction with lengthening of the P-R interval in the presence of apparently complete bundle-branch block in persons with gross disease of the heart: these periods of normal conduction tended to happen after rest. Baker brought about temporary disappearance of bundle-branch block by rest and also by administering oxygen to an old man with myocardial disease. In the case of the young man which I have investigated I feel that there is either an area of fibrosis interfering with one of the bundle branches or possibly a con-

\*It should be noted that the P-R interval in this tracing is only slightly shortened (0.1 second).

genital abnormality in the bundle-branch conducting system, e.g. bundle of Kent. There is no evidence, at the moment, in his case of any variation in the ventricular conduction.

#### SUMMARY

A case of bundle-branch block with a slightly shortened P-R interval in a normal young man is described.

Electrocardiograms were taken after deep breathing, pressure on the vagi, exercise, and after giving sodium trinitrini by mouth, and showed no change.

Injection of one-hundredth of a grain of atropine subcutaneously tended to elevate the T-waves in Leads II and III.

References are made to numerous theories on the mechanism of bundle-branch block in normal persons and also to cases described by other authors.

#### REFERENCES

1. Baeh, F.: *Quart. J. Med.* 23: 261, 1930.
2. Tung, Chen Lang: *AM. HEART J.* 11: 89, 1936.
3. Cohn, A. E., and Lewis, T.: *Proc. N. Y. Path. Soc.* 14: 207, 1914.
4. Drury, A. N., and Maekenzie, D. W.: *J. Physiol.* 80: 329, 1934.
5. Einthoven: *Arch. f. d. ges. Physiol. Bonn.* 122: 517, 1908.
6. Eppinger and Rothberger: *Ztschr. f. klin. Med.* 70: 1, 1910.
7. Gaskell: *J. Phys. Camb.* 4: 43, 1883.
8. Graybiel, A., and Sprague, H. B.: *Am. J. M. Sc.* 185: 395, 1933.
9. Hering, H. E.: *Arch. f. d. ges. Physiol.* 127: 155, 1909.
10. Holzmann, M., and Scherf, D.: *Ztschr. f. klin. Med.* 121: 404, 1932.
11. Kent, A. F. S.: *Quart. J. Exper. Physiol.* 7: 192, 1914.
12. Kent, A. F. S.: *Brit. M. J.* 2: 105, 1914.
13. King, J. T.: *Am. J. M. Sc.* 187: 149, 1934.
14. Lewis, T., and Master, A. M.: *Heart* 12: 209, 1925.
15. Pezzi, C.: *Arch. de mal du coeur* 24: 1, 1931.
16. Ritchie, W. T.: *Quart. J. Med.* 6: 47, 1912.
17. Sigler, L. H.: *Am. J. M. Sc.* 185: 211, 1933.
18. Von Deesten, H. T., and Dolganos, M.: *Am. J. M. Sc.* 188: 231, 1934.
19. Wedd, A. M.: *Arch. Int. Med.* 27: 571, 1921.
20. Wolferth, C. C., and Wood, F. C.: *AM. HEART J.* 8: 297, 1933.
21. Wolfe, L., Parkinson, J., and White, P. D.: *AM. HEART J.* 5: 685, 1930.
22. Wood, F. C., Jeffers, W. A., and Wolferth, C. C.: *AM. HEART J.* 10: 1056, 1935.

## COMPLETE HEART-BLOCK IN ACUTE RHEUMATIC FEVER

### CASE REPORT

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COMPLETE heart-block is but rarely encountered in acute rheumatic fever. In 1932, Wedd<sup>3</sup> reported one case of transient block with complete recovery, and reviewed recent literature. Since then there have been a few isolated case reports. In that paper<sup>3</sup> two instances of partial block in acute rheumatic fever were also described, and because of changes which occurred during the course of the disease it was suggested that such block might be on a functional basis and not necessarily dependent on structural change. Atropine was not tried in those cases, but later I cited an example of reduction by atropine in the degree of high-grade partial block which had followed a severe throat infection.<sup>4</sup> Recently Bruenn<sup>1</sup> has reported transient diminution by atropine of the prolonged conduction time in 19 of 22 cases of acute rheumatic fever in which the test was made, and he concluded that the conduction impairment of that disease was due, at least in part, to increased vagal tone. Such observations are of considerable interest in relation to those of Gross and Fried,<sup>2</sup> who found minimal changes in the conduction system in acute rheumatic fever. Vascular changes appeared to them more frequent and more conspicuous than exudative. It is possible that the relief of block by atropine might be partly due to increased coronary flow, such as occurs in the experimental animal, although the dilator action of atropine is seldom marked, and when present is probably part of vagal release. In a case of transient complete block which followed thrombosis of the right coronary artery, block did cease for a short period four to six minutes after the subcutaneous injection of 2 mg. of atropine, but this effect probably resulted from the fall in auricular rate from 75 to 65 beats per minute during the early stimulating phase of atropine action; when the auricular rate rose to 112 per minute a 2:1 block was established. The atropine response in the present case seems comparable to the termination by that drug of complete block that has been produced by digitalis,<sup>5</sup> and lends further support to the idea that a vagal factor is largely responsible for such block. Since this patient was of an unusually placid temperament and syncopeal attacks and block occurred only after physical strain, it would seem that in this case the origin of heightened vagal tone was in the heart, and not in the medulla, as Bruenn argued for his patients. The therapeutic importance of con-



sidering a functional factor in the heart block of acute rheumatic fever, and the possibility of its relief by atropine, is brought out in the following case history.

The patient, an unmarried woman forty-one years of age, was admitted to the hospital July 31, 1936. At the age of twenty-one years she had diphtheria. Recurrent attacks of tonsillitis had occurred previous to tonsillectomy in 1929. Several teeth had been extracted during recent years because of hypertrophic arthritis which had gradually developed in several finger joints. On July 4, she had gone swimming. She stated that she remained too long in the water and became chilled. Two days later she experienced severe pain in the right elbow, but thought it had resulted from a bruise. Two days after that, because of continued pain, she consulted an osteopath, who found her temperature to be 103° F. The elbow remained painful for about one week. During the middle of July there was pain and swelling in the right ankle joint. An ointment had been applied to the painful joints, and there were no signs of acute arthritis at the time of admission to the hospital. Throughout the entire month the patient frequently experienced profuse sweating, especially at night, and she knew that fever had been present at least part of the day. However, she had continued her work as a telephone operator up to the time she came to the hospital. For two days before giving up she noticed unusual shortness of breath on climbing a single flight of stairs. She also described throbbing of the heart, a feeling of weakness in the heart, and at times burning beneath the sternum. Three days before admission to hospital while on a long motor trip she complained of aching in the precordial region. During the last week of July giddiness and faintness occurred after going up stairs. On the evening of July 30, she consulted her local physician and while in his office fainted. The next morning she had another syncopal attack and was then sent to the hospital. No drugs had been administered.

When first seen the woman appeared critically ill. She was vomiting, and the skin was pale, cold, and wet. The heart sounds were of poor quality. The rate was about 50 per minute but the rhythm was irregular, with long intervals between some of the beats. The following morning she was quite comfortable. The only significant abnormal findings were in the heart. The heart appeared slightly enlarged to the left. A gallop rhythm was heard, and at the apex a faint systolic murmur. The rhythm was regular, with a rate of 96 per minute. The systolic blood pressure was 108 and the diastolic, 72. The temperature was normal. Blood examination showed a mild secondary anemia, and a leucocyte count of 16,800, of which 90 per cent were neutrophils. In the urine there was a strong trace of albumin, hyaline, and finely granular casts, and a few erythrocytes.

The patient continued free from symptoms until the afternoon of August 3, when following an enema a series of syncopal attacks occurred. Three generalized convulsive seizures were observed. After vomiting, a cold sweat of extreme degree appeared. Only an occasional heart sound could be heard; the radial pulse was imperceptible, and the blood pressure was not measureable. She was very pale, but there was no cyanosis. There was no prolonged loss of consciousness, and dyspnea was strikingly absent. That death was imminent was the opinion of all who saw her, and of the patient herself. Epinephrine, first 0.3 c.c. of 1-1000 solution, and five minutes later, 0.5 c.c. was injected intramuscularly without any beneficial effect, although the drug apparently caused some auricular slowing and an occasional ventricular response to an auricular impulse. Ten minutes after the second epinephrine injection, 2 mg. of atropine were injected deep into a deltoid muscle. After four minutes ventricular beats began to occur more frequently and an occasional beat came through to the wrist. Eleven minutes after atropine the cardiac mechanism became normal, and it remained so. The shock-like state passed off in about two hours.

The remainder of the patient's stay in the hospital was uneventful. No further syncopal attacks occurred, nor were there any other cardiac symptoms. The morning following the severe attack the heart rate was 64 per minute, and it continued within normal range. A sinus arrhythmia was often present. The apical murmur disappeared after the first few days. The blood pressure remained low, systolic 86

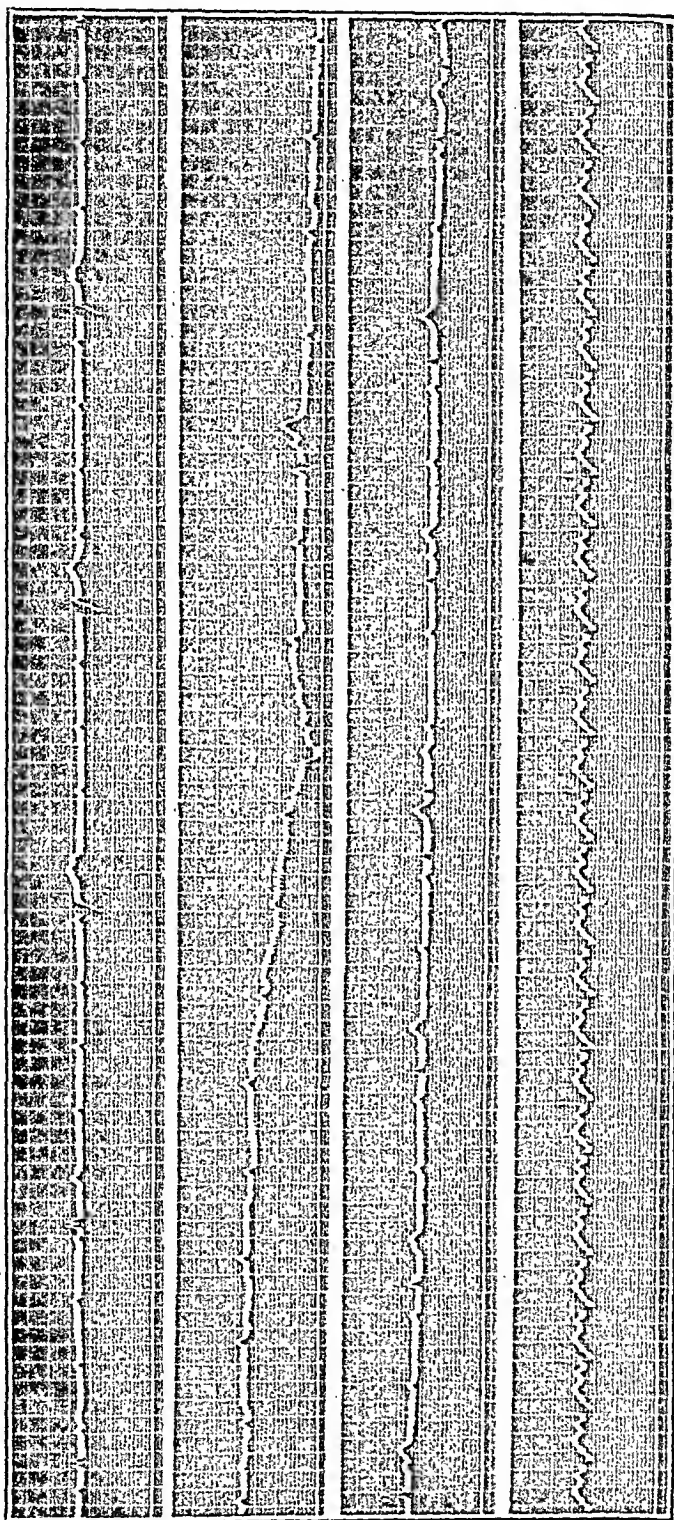


Fig. 1.—Line 1. Part of first record. Line 2. Shortly after the preceding, and during a mild convulsion; one recorded ventricular beat in 20 seconds. Line 3. After the second epinephrine injection. Line 4. 15 minutes after atropine. Time marker, 0.18 sec.

to 106, diastolic, 60 to 80. Fever ceased promptly under salicylate medication. Fluoroscopic examination on September 14 showed slight uniform enlargement of the heart, which was transversely placed. All electrocardiograms taken after the period of complete dissociation have shown intraventricular block, but a normal P-R interval.

## REFERENCES

1. Bruenn, H. G.: The Mechanism of Impaired Auriculoventricular Conduction in Acute Rheumatic Fever, *AM. HEART J.* 13: 413, 1937.
2. Gross, Louis, and Fried, B. M.: Lesions in the Auriculoventricular Conduction System Occurring in Rheumatic Fever, *Am. J. Path.* 12: 31, 1936.
3. Wedd, A. M.: *Complete Heart Block in a Case of Acute Rheumatic Fever.* Partial Heart Block in Acute Rheumatic Fever, *Clifton Med. Bull.* 18: 63, 1932.
4. Wedd, A. M.: Syncopal Attacks Associated With Partial Heart Block, *Clifton Med. Bull.* 20: 1, 1936.
5. Wedd, A. M.: Observations on the Clinical Pharmacology of Digitalis, *Bull. Johns Hopkins Hosp.* 30: 131, 1919.

# Department of Reviews and Abstracts

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## Selected Abstracts

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de Boer, S.: The Effect of Rauwolfine on the Heart and on Fibrillation of the Heart Chambers. *Cardiologia* 1: 1, 1937.

The heart rate of frogs, cats, and rabbits decreases after poisoning with rauwolfine.

The refractory period of the frog's heart increases after administration of rauwolfine.

In frogs there are disturbances of the heart rhythm comparable with those following poisoning by digitalis compounds.

Rauwolfine poisoning produces artificial changes of the heart rhythm in the frog.

After poisoning of the frog's heart with rauwolfine the intraventricular conductivity is delayed.

Rauwolfine does not prevent auricular or ventricular fibrillation either in cats or in rabbits. (If there should be any influence at all of rauwolfine on auricular or ventricular fibrillation this would be insignificant.)

AUTHOR.

Martini, P., and Fr. Grosse-Brockhoff: Action of Strophanthin in Fever. *Arch. f. exper. Path. u. Pharmacol.* 180: 597, 1936.

Action of strophanthin was determined in rabbits suffering from fever experimentally produced with staphylococcus injections. It was found that these animals gave less response to the drug than normal rabbits.

L. N. K.

Lederer, E.: Capillary Circulation Studies. II. Action of Certain Drugs on the Circulation. *Arch. f. exper. Path. u. Pharmacol.* 182: 372, 1936.

Thyroxin subcutaneously causes capillary dilatation and acceleration of flow. Adrenalin and strychnine slow the flow.

L. N. K.

Lissak, K., and Kobas, F.: Symptomatology of Anaphylactic Shock in the Dog and the Mechanism of Its Production. *Arch. f. exper. Path. u. Pharmacol.* 182: 504, 1936.

In shock, both anaphylactic and histamine, the blood pressure drops, the spleen shrinks, and the bronchial muscles contract. This occurs even when the adrenals are removed and the spleen is denervated. This indicates a direct humoral action in smooth muscle, as was demonstrated on isolated strips of spleen. The sensitivity of the dog to choline and acetylcholine is increased during sensitization to foreign protein, but the sensitivity to histamine is unchanged.

L. N. K.

Went, S., and Lissak, K.: The Rôle of Choline in the Production of Shock in the Guinea Pig Heart. *Arch. f. exper. Path. u. Pharmacol.* 182: 509, 1936.

The guinea pig heart during anaphylactic shock liberates a substance into the perfusate which inhibits the frog's heart. (This inhibition is abolished by atropine.)

This perfusate has no effect on the leech preparation (used as a specific for acetylcholine). The acetylyzed perfusate works both on the frog heart and on the leech preparation. The choline content of the heart in anaphylactic shock decreases, whereas histamine remains unchanged. The liberated substance, from these studies, is thus shown to be choline.

L. N. K.

Weinberg, J.: Studies of Central Vasomotor Regulation. Part II. Histamin. Arch. f. exper. Path. u. Pharmacol. 185: 235, 1937.

In trained, previously trephined, unanesthetized dogs, injections of histamine 0.01 to 0.1 mg. into the lateral ventricles gave consistent rises in blood pressure of from 20 to 56 mm. Hg lasting from fifteen to thirty-eight minutes. Twenty injections in all were given to eight dogs. One smoked drum record of the blood pressure obtained as usual from a superficial branch of the saphenous artery is offered. The rise in blood pressure preceded vomiting and defecation and the animals did not appear to be disturbed by the injection. In two instances prolonged fall in pressure followed the rise. The author believes that these studies make it necessary to reconsider Cushing's investigations in man which tended to show that histamine had no effect when given intracranially.

J. M. S.

Ferrannini, A.: Action of Strophanthin on the Purkinje Fibres on the Dog Heart. Arch. internat. de pharmacodyn. et de therap. 53: 501, 1936.

The meehanogram optically recorded and the electrogram of isolated Purkinje fibers were studied. It was found that strophanthin increased the amplitude and rate of the beat of the Purkinje fibers and altered the contour of its electrical curve. This drug also leads to arrhythmias, alternans, and contracture.

L. N. K.

Tournade, A., and Chevillot, M.: Is the Action of Vaso-Dilator Nerves Only a Matter of Liberation of Acetylcholine? Compt. rend. Acad. d. sc. 204: 1586, 1937.

The purpose of this short note is to add to the literature two instances in which the effects of faradization of the nerve of Hering had different effects from injection of acetylcholine. The observations were as follows:

1. The left kidney of Dog I was perfused through the cervical vessels of Dog P. Stimulation of the right nerve of Hering of Dog I was followed, not only by fall in blood pressure and slowing of the heart, but as well by *vasodilatation* of the renal vessels. A similar reaction was obtained with 0.05 mg. acetylcholine injected directly into the renal artery. Then the perfusing Dog (P) received 10 mg. of atropine. Now electrical stimulation of the nerve was followed, as before, by renal *vasodilatation* while the same dose of acetylcholine was followed by marked *vasoconstriction*.

2. Injection of 0.5 mg. ergotamine directly into the renal artery resulted in constriction of that organ's vessels and a rise of 5 mm. Hg in the systemic pressure of Dog P. Faradization of the nerve of Hering was now without effect while intra-arterial injection of acetylcholine was followed by *vasodilatation*. When acetylcholine was injected into the saphenous vein of Dog I, fall of blood pressure did not evoke constriction of the renal vessels perfused by Dog P. These two observations suggest that ergotamine has paralyzed vasoconstriction and dilatation due to nervous stimuli, while injection of acetylcholine can still produce *vasodilatation*.

The authors assert that the theory of humoral transmission of nervous impulses is important, but believe that this mechanism is not the only one for transmission of

nervous impulses. They believe that physical transmission is at least of equal importance. They recall the usual objections to their form of experiment, namely, that amount of acetylcholine and site of liberation may differ from normal.

J. M. S.

Thiel, K.: Action of Artificial Breathing. *Med. Klin.* 32: 633, 1936.

Dogs were asphyxiated under morphine anesthesia until no flow could be measured in the carotid artery with a Rein stromuhr. The heart was revived by massage and by artificial breathing. While blood flow quickly returned to normal, the electrocardiogram remained abnormal for some time. The use of O<sub>2</sub> rich air did not affect the rate of restoration. Cardiazol and sympatol, however, did.

L. N. K.

Gotsev, T.: Vasomotor Centers I. *Pflüger's Arch. f. d. ges. Physiol.* 237: 609, 1936.

The author presents the effect of a large number of vasomotor substances determined before and after decapitation of dogs. No difference was noted. The conclusion is arrived at that these vasomotor centers play little rôle in the action of these substances. Among substances used were pituitary derivatives, acetylcholine, lactic acid, ergotamine, caffeine, sodium benzoate, and histamine.

L. N. K.

Gollwitzer-Meier, Kl, Kramer, K., and Krüger, E.: Action of Adrenalin on the Energy of the Heart. *Pflüger's Arch. f. d. ges. Physiol.* 237: 639, 1936.

Adrenalin (1/200 to 1/100 mg.) increases the gaseous metabolism of the heart about 350 per cent over normal. The peak of gaseous metabolism lags behind the peak of work. Hence, there is an anoxybiotic phase of increased work. The action of adrenalin on gaseous metabolism is decreased in the presence of anoxemia, but unaffected by the level of venous flow and arterial resistance. The increased metabolism is in part brought about by increased coronary flow but chiefly by increased A-V O<sub>2</sub> difference.

L. N. K.

Puddu, V.: The Action of Cardiac Nerves. *Pflüger's Arch. f. d. ges. Physiol.* 238: 467, 1937.

The author found that there are two phases to the changes in the electrocardiogram following stimulation of the sympathetic nerves in the dog, and further that the right and left nerve have opposite effects on the ventricular complex. Both nerves appear to go to all parts of the hearts. He could not demonstrate that sympathin played any rôle.

Following complete A-V block on cutting both bundles in the dog, vagus stimulation causes a slowing of the idioventricular pacemaker. The author attributes this to liberation of acetylcholine-like substances transported to this part of the heart.

L. N. K.

Sachs, A.: The Effect of Cholin Bodies on Auricular Systole. *Cardiologia* 1: 74, 1937.

The choline derivatives which were investigated had similar actions. The smallest doses required to diminish the force of auricular contraction were 0.1 acetylcholine, 0.25 doryl, 1 cholinechloride, 50 cholazyl, in 40 c.c. of the fluid in which the auricular

muscle was suspended. Smaller doses increased the force of contraction, and still smaller doses were ineffective. With large doses slowing of the rate of contraction was only observed associated with diminution of force. Frequently, however, the force of contraction was diminished without slowing. No reduction of tonic activity of the auricular muscle was observed. The action of these compounds depends not so much on the absolute amount but on the effective concentration inside the cell. This applies to acetylcholine and doryl, and to a smaller extent to cholinechloride and cholesteryl. It is suggested that this explains the variable responses obtained with equal doses on the same auricular strip.

The auricular strip of the rabbit's heart is suitable for the assay of unknown acetylcholine-like compounds in moderate but not in the smallest concentrations.

AUTHOR.

Zimmermann, O.: Pathogenesis of Gonococcal Arthritis, Endocarditis, and Sepsis. *Wien. klin. Wchnschr.* 49: 1518, 1936.

A case report is presented with a late involvement of the heart in the form of inflammatory perforation of the aorta through the ventricular septum into the right ventricle. There was a nonarthritic involvement eighteen years after gonorrheal urethral infection and the cardiac complication occurred six years after the joint involvement. This last was associated with mitral, aortic valvulitis, and gonorrheal sepsis. The aortic valvulitis was superimposed on a congenital bicuspid valve with stenosis.

L. N. K.

Holzöhner, E.: The Respiratory Pulse (Cardiopneumogram) and the Return Flow of Blood to the Heart. I. Its Relation to Posture in Man. *Ztschr. f. Biol.* 97: 409, 1936.

A record on a man taken from the air passages during respiratory arrest showed a decrease in lung volume occurring at the onset of ejection of the heart and an increase in lung volume at the end of the ejection period. The latter indicates an augmented venous return flow into the chest greater than arterial outflow, indicating a systolic suction. In the extended posture the suction action is less; in the flexed posture, it is augmented. The greatest suction action occurs on reclining and in deep inspiration.

L. N. K.

Raab, W., and Friedman, R.: The State of the Circulatory Tree in Vegetarians and Alcoholics. *Ztschr. f. klin. Med.* 130: 595, 1936.

It was found that alcohol excess has no detrimental effect on arteriosclerosis and hypertension. The avoidance of meat does not check the development of arteriosclerosis but blood pressure and central vasomotor excitability is decreased. This is especially marked if eggs and milk products are also eliminated.

L. N. K.

Fabian, G., and Scriba, J.: The Determination of the Basedow Heart by the Dyspnea Test. *Ztschr. f. klin. Med.* 130: 773, 1936.

CO<sub>2</sub> dyspnea is produced and the relation of maximum depth to the rate of breathing is determined. This was done in 33 patients with hyperthyroidism. The older the individual the more heart involvement present; the same relationship holds with regard to the increase in basal metabolism and the duration of the hyperthyroid state.

L. N. K.

Wezler, K., and Goyert, K.: A Method of Demonstrating the Action of the Blood Pressure Regulator Nerves in Man. *Ztschr. f. Kreislaufforsch.* 29: 241, 1937.

The authors made the tests by determining in optically recorded pulse curves (1) the period of free oscillation of the carotid artery (from the duration of the first dip in the peak of the carotid pulse times 2), (2) the ratio of the pulse wave velocity in muscular arteries (viz. brachial-radial) over that in elastic arteries (viz. aorta-iliac) and (3) the ratio of duration of systole to cycle length in the carotid pulse. The first of these is used as an index of the magnitude of the stimulus. It varied inversely with the endovascular pressure (and hence also inversely with the pulse wave velocity). The second is used as an index of the state of contraction of the muscles in the media of the muscular arteries. The third is used as an index of the reflex action on the heart. A pressure drop in animals causes an acceleration of the pulse and an increase in the systole/cycle ratio. The authors have demonstrated that reflexes operate not only on heart and peripheral blood vessels but also alter the elasticity of the larger arteries. In a single individual where five separate sets of readings were obtained, it was found that as free oscillation in the carotid lengthened, the ratio of pulse wave velocities decreased, the heart accelerated and systole/cycle ratio lengthened. Similar correlations could be made out on comparing a group of normal individuals, but there was a difference between the standing and prone positions. The authors demonstrated that a high sympathetic tone in arteries was associated with a low sympathetic tone in the heart due to reflexes from the blood pressure regulators.

L. N. K.

Tietze, K.: Action of Baths on Circulation Time in Man. *Ztschr. f. Kreislaufforsch.* 29: 354, 1937.

The method of Matthes and Malikiosis for circulation time was used. It consists of holding the breath as long as possible after taking a breath of a CO<sub>2</sub> rich atmosphere. The O<sub>2</sub> saturation of arterial blood in the ear and the hand is measured by an indirect method in the unopened blood vessels and the time from the first breath until the blood begins to show an increase in O<sub>2</sub> saturation is used as a measure of circulation time from the lung to the ear and from the lung to the arm. Hot baths caused a shortened circulation time and cold baths increased the circulation time. The same effect was produced by cold and hot applications to one extremity. Similar changes with the baths were found in minute volume flow determined by the arteriovenous difference of O<sub>2</sub> (where the venous blood obtained is not stated) using the Fick principle.

L. N. K.

Schlomka, G., and Vienken, W.: Studies on the Physiological Irregularities of the Heart Beat. II. The Relation Between Respiratory Arrhythmias and Respiratory Alterations in Electrocardiographic Configuration. *Ztschr. f. Kreislaufforsch.* 29: 194, 1937.

The authors determine the type index of the electrocardiogram by the following formula:

$$I = \frac{(O_1 - U_1) - (O_2 - U_2)}{(O + U) \text{ max.}}$$

where O<sub>1</sub> and O<sub>2</sub> are the magnitudes of the major upright phase of QRS in Leads I and II, U<sub>1</sub> and U<sub>2</sub> are the magnitudes of the major downward phase of QRS in these leads, and (O and U) max. is the sum of the major upright and major inverted phases of QRS in either Lead I or III, depending on which value is the largest. The authors also determined the variation of the type index during the respiratory cycle



by the difference between the inspiratory and expiratory type index. The analysis is based on 38 electrocardiograms. They argue that this index gives evidence of the functional state of the heart. On this basis, they attribute changes in the electrocardiogram during respiration to hemodynamic alterations of the heart. (These interpretations are speculative and need further support.)

L. N. K.

Schlomka, G., and Theiss, O.: Determination of the Relative Duration of Systole.

II. Relative Duration of Systole in Hypertension. *Ztschr. f. Kreislaufforsch.* 29: 385, 1937.

The correlation factor between the cycle length and the cube root of the Q-T interval was determined in 287 cases. In general the relative duration of systole is longer in hypertensives than in normals, and this lengthening is proportional to the pressure level. Aging causes a lengthening in systole in hypertensives as well as in normals. Further, the range of systolic duration at different heart rates is greater in hypertensives than in normals. The lengthening of systole is viewed by the authors as the result of insufficiency of the heart, which acts to permit a greater output than would otherwise be possible.

L. N. K.

v. Zárday, I.: Unusual A-V Conduction Disturbances. *Ztschr. f. Kreislaufforsch.* 29: 208, 1937.

A case of short P-R interval and increased duration of QRS is reported in which precordial leads were used to analyze the disturbances further. These indicated early stimulation of the right and late stimulation of the left ventricle. This is attributed, as has been done previously, to conduction to the right ventricle via the bundle of Kent or some other abnormal junctional bridge. When the heart rate was accelerated, it was found that P-R lengthened and QRS duration shortened but the duration from the beginning of P to the end of QRS was unchanged. This is interpreted as indicating block in the abnormal junctional bridge.

L. N. K.

Steinmann, B.: The Electrocardiogram in Carbon-Monoxide Poisoning. *Ztschr. f. Kreislaufforsch.* 29: 281, 1937.

Twenty-one of the thirty cases of carbon-monoxide poisoning showed electrocardiographic evidence of myocardial damage. In nine cases with mild poisoning, no electrocardiographic abnormalities were seen. These changes in the electrocardiogram are reversible. No instance of persistent damage could be demonstrated. The changes were chiefly depression of the S-T segment and flattening of the T-wave. These are attributed to the anoxia.

L. N. K.

Riseman, Joseph E., and Brown, Morton G.: The Sedimentation Rate in Angina Pectoris and Coronary Thrombosis. *Am. J. M. Sc.* 194: 392, 1937.

The corrected sedimentation index was studied in 113 persons: 37 with coronary thrombosis, 55 with angina pectoris, and 21 apparently normal persons between the ages of forty-five and seventy.

Elderly individuals, without any evidence of disease, may have a corrected sedimentation index slightly higher (up to 0.70) than the accepted normal for young adults.

A moderate elevation of the corrected sedimentation index (0.73 to 1.38) was found in over half of the patients with angina pectoris. There is reason to believe that attacks of angina pectoris occasionally result in myocardial damage.

An elevated sedimentation rate is one of the most constant manifestations of coronary thrombosis. The fastest rates were observed between the fourth and twelfth days after the onset of symptoms.

In two-thirds of the cases the rate was considerably greater than that seen in angina pectoris; this may be of value in differentiating between angina pectoris and coronary occlusion during the first two weeks after the onset of an attack.

The sedimentation rate reflects the course of the disease and is an aid in following the progress of the patient but is of little or no aid in the prognosis of the acute attack.

The mortality of patients discharged from the hospital with fast sedimentation rates was twice as great during the first year after discharge as that of patients discharged with low or normal rates. It is advisable to continue bed rest until the sedimentation index either returns to normal or shows no further progression towards normal.

AUTHOR.

Palmer, J. H.: The Size of the Heart After Coronary Thrombosis. *Canad. M. A. J.* 36: 387, 1937.

Enlargement of the heart was found by radiological methods in 64 per cent of a series of 200 patients who had survived an attack of coronary thrombosis. Doubtful enlargement, 16 per cent of the series, was for the purpose of this paper added to the normal group, but the high incidence of enlargement in published necropsies favors the view that these doubtful hearts are in reality enlarged.

The factors causing enlargement after coronary thrombosis are discussed. By far the most important proved to be hypertension, which was held to be the single or predominant cause in more than 80 per cent of all cases with enlargement.

Disease of the coronary arteries, either the actual thrombosis with its resulting infarction or the underlying arteriosclerosis, led to increase in the size of the heart in a total of 11 cases (8.6 per cent). Of these, 4 (3.1 per cent) had cardiac aneurysm, 3 (2.4 per cent) had a bundle-branch lesion, and the remaining 4 (3.1 per cent) had enlargement, apparently due to chronic myocardial ischemia alone.

No example of so-called acute dilatation of the heart was discovered among 27 patients examined radiologically within a month of the attack. Congestive failure, which was not seen in hearts of normal size, seldom led to an appreciable increase in the degree of enlargement.

About one-third of the patients (36 per cent) failed to show or to develop enlargement, though watched over periods averaging more than three years following the first attack of coronary thrombosis; and this number included several with recurrent attacks.

AUTHOR.

Palmer, J. H.: The Prognosis Following Recovery From Coronary Thrombosis, With Special Reference to the Influence of Hypertension and Cardiac Enlargement. *Quart. J. Med.* 6: 49, 1937.

The prognosis, with special regard to the influence of hypertension and cardiac enlargement, has been studied in 212 cases of coronary thrombosis which survived the attack by three months.

More than one-fourth were able to lead fairly active lives. In the remainder, angina of effort and dyspnea on exertion (including chronic congestive failure) were the most important symptoms causing restriction of activity or invalidism, and these were operative in almost equal proportion. The active group lived longer following the attack than the restricted.

The onset and incidence of angina after coronary thrombosis were not related to the height, or changes in the height, of the blood pressure, or to the size of the heart. Angina of every grade of severity, including that compatible with a fairly active life, occurred in 39 per cent of cases prior to the attack and in 58 per cent of cases following it; in less than 10 per cent did prior angina fail to recur after the attack. The presence of subsequent angina did not affect the average duration of life.

The incidence of dyspnea severe enough to cause restriction of activity followed closely the incidence of cardiac enlargement. Hypertension was not more frequent in the dyspneic group than in the whole series.

Congestive failure, which affected 13 per cent of the series, was found only in patients with enlarged hearts.

Subsequent attacks of coronary thrombosis occurred in 28 per cent, about half of them during the first two years. The incidence of these attacks was unrelated to the height of the blood pressure, but was somewhat higher in cases with enlargement than in those with hearts of normal size. About one-fifth of these subsequent attacks were fatal.

The duration of life following the attack averaged 4.2 years in 65 cases known to have died. Hypertensives appeared to have a somewhat more favorable outlook in this regard than nonhypertensives. The groups with cardiac enlargement and with congestive failure showed a slight reduction in the duration of life, which was, however, unaffected in the average by further attacks of coronary thrombosis.

A statistical table is presented showing the rate of survival based on experience of the series.

Short summaries are given of the histories of eleven patients (5 per cent of the series) known to have lived for more than ten years following the attack.

Blood pressure changes and the height of the blood pressure following recovery from an attack of coronary thrombosis are on the whole of little significance.

Cardiac enlargement is a most important factor in causing restriction of activity; the expression of its influence is dyspnea on exertion, and in the most severe cases congestive failure.

The probability that following recovery from an attack of coronary thrombosis a patient will be able to lead a fairly active life is almost twice as great in those with normal sized hearts as in those with cardiac enlargement.

AUTHOR

Kisch, Bruno: Interpolated Ventricular Extrasystoles. *Cardiologia* 1: 88, 1937.

Report of records of a case with interpolated ventricular extrasystoles. The delayed conductivity of the contraction following the interpolated systole is the greater when (a) the general conductivity in the heart is less efficient, and (b) when the time between extrasystole and the following contraction is less.

The delayed conductivity following an interpolated extrasystole is the same phenomenon as in what is known as "Wenckebach'sche Perioden." The occurrence of the pre-ventricular wave (described in an earlier paper as "Zwischenzacke") in the electrocardiogram of a heart beat with greatly delayed conductivity is further evidence that these pre-ventricular waves ("Zwischenzacken") are significant of abnormal conductivity.

AUTHOR

Bernheim, Alice R., and London, Isabel M.: Arteriosclerosis and Thromboangiitis Obliterans: Report of Cases and Treatment. J. A. M. A. 108: 2102, 1937.

Ninety-nine cases of arteriosclerosis of the extremities and 54 cases of thromboangiitis obliterans were treated. Relief of vasospasm was considered important, because it is an underlying process in both diseases. Treatment of vasospasm consisted in the use of measures to eliminate the following causes: tobacco, improper diet, worry, undue physical exertion, and cold. An increase in blood viscosity was found in patients with arteriosclerosis as well as in those with thromboangiitis obliterans. For this reason, sodium citrate was given in all cases presenting severe symptoms. Decreases in viscosity of from 1 to 2 points followed the intravenous injection of 250 c.c. of a 2 per cent solution of sodium citrate. There was improvement in 83 of the cases of arteriosclerosis, and in 43 of the cases of thromboangiitis obliterans.

H. M.

Allen, Edgar V., and Crisler, George R.: The Result of Intra-Arterial Injection of Vasodilating Drugs on the Circulation: Observations on Vasomotor Gradient. J. Clin. Investigation 16: 649, 1937.

The vasodilating drugs, papaverine hydrochloride, acetyl B-methylcholine (mecholy), and histamine, cannot be "fixed" in an extremity to any great degree by injecting them into the lumina of arteries supplying the extremities. For example, the results on the temperature of the toes of the right foot of injecting mecholy into the right femoral artery are about the same as those which follow the injection of mecholy into the brachial artery.

The lower extremities contrasted to the upper extremities are relatively very refractory to vasodilating agents, as shown by the fact that the vasodilating drugs used produced moderate to marked increases in temperatures of the fingers and no increase or very little increase in the temperatures of the toes regardless of whether papaverine and mecholy were injected into the femoral artery, into the brachial artery, or intravenously or intramuscularly. This refractoriness of vasodilatation in the lower extremities seems intimately associated in some way, as yet unexplained, with the much higher incidence of chronic occlusive arterial diseases in the lower extremities as contrasted with the incidence in the upper extremities.

AUTHOR.

Springorum, W.: The Influence of Local Thermal Stimulation Upon the Flow of Blood Through the Skin. Arch. f. d. ges. Physiol. 238: 517, 1937.

By placing a small Rein stromuhr on the artery leading to the ear of a dog, a technique previously described by the author and abstracted a few months ago in this journal, Springorum was able to follow changes in the flow of blood to the ear while immersing it in cold or hot baths. He studied this problem anew because most of the methods for estimating change in blood flow to the skin have been indirect ones while this is direct.

Large dogs were lightly anesthetized, usually with morphine pernocton, sometimes with chloralose. The drug used for anesthesia made little difference but as anesthesia was gradually deepened the reaction to heat was first lost, then that to cold.

The importance of the work lies in the quantitation of the reactions and the timing of their appearance following the stimulus through the use of optical records of unusual excellence. The results are somewhat as follows: (1) Increase in flow on raising the temperature from 20° to 40° is about four to six times. Decrease

in flow from room temperature to 13° may amount almost to complete stoppage. (2) Repeated application of heat tends to reduce progressively the speed of development of and ultimate height of the reaction. (3) Many times reactions to heat were slight and occasionally even absent. The circumstances under which these failures occurred were not quite clear to the author. The reaction to cold was apparently more constant. (4) The increase in flow of blood in response to warmth begins after a latent period of ten to twenty seconds and takes place very abruptly. Decrease in flow with cold begins at once and progresses slowly and steadily.

The author concludes, therefore, that the one reaction cannot be thought of as the reversal of the other and that the mechanisms of inducing the responses must consequently be quite different. He can say nothing about denervated preparations since he was unable to verify completeness of denervation. The carrying out of this procedure would seem a useful complement to the present work. He concludes tentatively that nervous elements must play a large part in regulating the reactions to local thermal stimuli.

J. M. S.

Müller, A.: *Thrombophlebitis and Its Treatment With Ambulant Compression Bandages.* Med. Klin. 33: 793, 1937.

The author discusses the parts played by local inflammation and slowing of the blood stream in thrombosis and appears to believe that slowing of the stream is more important. After reviewing literature of figures on the outcome of phlebitis, it became apparent that the use of Fischer's compression bandage gave better results and he therefore began to use it. Out of several hundred patients, 83 were thromboses of the deep veins, and 12 were postoperative. Only 2 deaths occurred, both with pulmonary infarcts. The author states that long standing cases with considerable edema and induration often cleared up in a very short time—two to five days—with almost immediate disappearance of pain. He emphasizes the fact that it can be applied over ulcers to great advantage and appears to be especially useful in aborting early painful thromboses.

The rationale is making smaller the venous cross-section and therefore the flow of blood more rapid. He recommends the use of stiff sized cloth for compression bandages wrapped over softer supporting bandages and wads of padding for the bony prominences of foot and tibia. The knee is left free except perhaps for stockinette and the thigh is bandaged tightly with an elastic bandage. The compression bandage must be as tightly wrapped as possible without stopping arterial flow. Unless there are other contraindications the patient is kept up and active.

J. M. S.

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